# Asphyxia at birth and neonatal neurologival morbidity

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# ASPHYXIA AT BIRTH AND NEONATAL NEUROLOGICAL MORBIDITY

M. J. DIJXHOORN

# ASPHYXIA AT BIRTH
# AND
# NEONATAL NEUROLOGICAL MORBIDITY

STELLINGEN

1. De meeste pasgeboren kinderen met neurologische afwijkingen hebben een normaal geboortegewicht.

2. Gegeven een adequate verloskundige begeleiding, is bij à terme geboren kinderen met een normaal geboortegewicht asfyxie bij de geboorte geen belangrijke oorzaak van neurologische afwijkingen in de neonatale periode.

3. Het foetale hartactiepatroon ante partum is sterker gecorreleerd met de neurologische toestand van het kind dan de zuurgraad van het navelstrengbloed.

4. pH, bloedgas- en zuur-base- variabelen bij de geboorte correleren niet beter met de neurologische toestand van de pasgeborene dan de Apgar scores.

5. Bij vroeggeboren en/of in groei vertraagde kinderen kan maternale alkalemie tijdens de bevalling een nadelige invloed hebben op de bloedgaswaarden en het zuur-base evenwicht in het navelstrengbloed.

6. De hypothese dat niet ontdekte episoden van zuurstoftekort tijdens de intrauteriene ontwikkeling neurologische afwijkingen bij het kind veroorzaken dient getoetst te worden.

7. Periodieke registratie van de positie van de testes vanaf de geboorte is voldoende om retractiliteit aan te tonen. Daarmee kan een groot aantal onnodige behandelingen van "niet-scrotale testes" worden voorkomen.

8. Gezien het hoge herhalingsrisico van vroeg optredende toxicose en foetale groeivertraging is in voorkomende gevallen profylactische acetylsalicylzuurtoediening bij een volgende zwangerschap geïndiceerd.

9. De pijngrens tijdens de bevalling wordt verlegd op het moment dat deze bereikt is.

10. In de wetgeving van Zuid-Afrika behoort zwart op wit te staan dat wit niet op zwart mag slaan.

11. Ondanks de grote interindividuele spreiding in foetale bewegingsfrequentie verdient één ondergrens van normaal de voorkeur boven individuele normaalwaarden.

12. Bij de in groei vertraagde foetus gaan veranderingen in navelstrengbloedstroomprofielen in het algemeen ongeveer drie weken vooraf aan het optreden van afwijkingen in het foetale hartactiepatroon.

13. Hoe dikker het medisch dossier hoe slechter het gelezen wordt.

Stellingen behorend bij het proefschrift "Asphyxia at birth and neonatal neurological morbidity". Marius J. Dijxhoorn, 10 december 1986.

RIJKSUNIVERSITEIT TE GRONINGEN

# ASPHYXIA AT BIRTH AND NEONATAL NEUROLOGICAL MORBIDITY

PROEFSCHRIFT

ter verkrijging van het doctoraat in de Geneeskunde
aan de Rijksuniversiteit te Groningen
op gezag van de Rector Magnificus Dr. E. Bleumink
in het openbaar te verdedigen op
woensdag 10 december 1986 des namiddags te 4.00 uur
door

MARIUS JOHANNES DIJXHOORN

geboren te Curacao

1986
DRUKKERIJ VAN DENDEREN B.V.
GRONINGEN

Promotores: Prof. Dr. H. J. Huisjes
Prof. Dr. B. C. L. Touwen
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*Chapter 1*

# INTRODUCTION

Is birth asphyxia a major factor in the aetiology of neurological dysfunction in the neonate? Are there certain obstetrical "risk" populations which are more prone to the damaging effects of asphyxia? This thesis reports a study performed to answer these questions. Severe perinatal asphyxia can result in death in utero or in neonatal death. In infants who survive such a serious insult perinatal asphyxia may result in "hypoxic-ischaemic" brain injury, which is one of the most important problems originating in the perinatal period and which accounts for a large percentage of neurological deficiencies in later life (Kreusser & Volpe 1984).

As the name "hypoxic-ischaemic" brain injury implies, the effects of asphyxia are due to deprivation of oxygen (hypoxia), either by hypoxaemia (deficient oxygenation of cerebral blood) or ischaemia (deficient blood perfusion of the brain) (Brann & Dykes 1977, Kreusser & Volpe 1984). Hypoxia is difficult to assess directly in the human fetus. Due to this limitation in human studies many indicators have been used as a basis for inferring that "asphyxia" has occurred. The wide variety of often inaccurate or imprecise definitions used makes it difficult to interpret scores of papers on the subject of "birth asphyxia".

The term asphyxia means literally pulselessness, emphasizing the reduction of pulsation and tone in the umbilical cord, leading to diminished oxygen supply to vital fetal tissues. Physiologists define asphyxia as a lack of oxygen with an excess of carbon dioxide. The combination of hypoxaemia and reduced blood flow will lead to oxygen deprivation, not only in the brain but in all fetal tissues, and anaerobic metabolism will begin. Lactic acid production will increase, the buffer base value will decrease and the fetal blood pH will fall. These measurable biochemical consequences of hypoxia in the umbilical cord, therefore, seem to

form a valuable indication of "asphyxia present at birth". However, acidaemia indicates the presence of tissue hypoxia somewhere in the fetus, not necessarily in the brain, and a close relationship with hypoxic brain damage needs to be demonstrated. Besides abnormal umbilical cord acid-base values (Beard & Rivers 1979), low Apgar scores (Nelson & Ellenberg 1981) and the presence of meconium stained amniotic fluid (Nelson & Broman 1977) have been used as indicators to define groups of asphyxiated neonates in studies of neonatal pathophysiology. The degree to which these clinical signs of asphyxia at birth are related to the neonatal neurological condition or to later intelligence and motor status is uncertain. The literature on this subject is equivocal and confusing; it will be reviewed in Chapter 2.

Some well-known clinical observations, such as persisting low Apgar scores (Nelson & Ellenberg 1981), delayed spontaneous respiration (Scott 1976), failed resuscitation for prolonged periods of time (Mulligan et al. 1980), neonatal seizures (Dennis & Chalmers 1982) etc. which indicate severe asphyxia in the neonatal period are important predictors of severe mental or neurological handicap. Nevertheless, most authors stress that there is a good chance that the surviving infants will develop normally. Most asphyxiated babies who show neurological abnormalities soon after birth recover completely (Nelson & Ellenberg 1981, Scott 1976).

An evaluation of the central nervous system (CNS) of the newborn is important because the CNS is particularly vulnerable to permanent damage due to metabolic- and circulatory disturbances and is of primary importance for the quality of further life. A neonatal neurological examination assesses the condition and eventual dysfunctions of the neonatal brain. The neonatal neurological condition has a certain predictive value because it is correlated to the later development of the CNS (Touwen 1981). Neonatal neurological condition is not often chosen as an indicator of neonatal morbidity, although adverse influences during pregnancy, labour and delivery were found to be related to neonatal neurological dysfunction (Prechtl 1968). The duration of the neonatal neurological abnormalities is a useful factor in identifying infants at greater risk for sequelae (Sarnat & Sarnat 1976).

The present study was designed to establish relationships between measurable indices of asphyxia at birth and the neonatal neurological condition. The null hypothesis can be formulated as : asphyxia at birth is a main cause of neonatal neurological dysfunction. This hypothesis is dealt with in Chapters 4, 5, 6 and 7. In Chapter 2 a description of known causes of brain damage, other than asphyxia, is given. The reliability of the indices used to measure asphyxia at birth, especially in relation to the neurological outcome, will also be discussed with reference to literature. Our own data in this study are derived from the Groningen Perinatal Project (GPP), which is a prospective longitudinal cohort study of infants born between 1975-1978 at the Obstetrical Department of the University Hospital in Groningen. In Chapter 3 the method of neurological investigation, the classification of the neurological and obstetrical data and the definition of the different study groups will be discussed.

The investigation to test or reject the aforementioned hypothesis was performed on different selected groups. It is known, for instance, that small-for-dates infants (<10th birth weight centile) (Huisjes et al. 1980, Huisjes et al. 1981) and preterm infants (<37 completed weeks of gestation) (Huisjes et al. 1980, Westgren et al. 1984) carry a higher risk than appropriate-for-dates (AFD) full-term infants.

In Chapter 4 the relationship between umbilical cord acid-base values and neonatal neurological morbidity is investigated in full-term AFD vaginally-born infants. A combination of measurable indices of asphyxia at birth might provide more valuable prognostic indications with respect to the neonatal neurological condition than either index alone. Therefore, such combinations of indices are investigated in the same study group in Chapter 5. In Chapters 6 and 7 the same relationships will be investigated in full-term SFD and preterm (AFD and/or SFD) infants respectively. It is emphasized to take the maternal acid-base state into account simultaneously with the assessment of the fetal scalp or umbilical cord acid-base value, as will be discussed in Chapter 2. Special attention is paid to the pH and base excess gradient between the mother and the fetus ($\Delta$pH and $\Delta$BE). One of the possible maternal acid-base disturbances which may have an adverse effect on the

fetus is maternal alkalosis. Chapter 8 reports an investigation into the effect of severe maternal alkalosis on the umbilical and acid-base status of the newborn which is mostly the result of hyperventilation during labour. Chapter 9 contains the general discussion and the conclusions.

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*Chapter 2*

# REVIEW OF THE LITERATURE

## 2.1. Introduction

There is little consensus in literature over the extent to which neurological problems in the perinatal period and/or neurological morbidity in later life are attributable to perinatal asphyxia. To answer this question properly we must have an understanding of the epidemiology of neurological handicaps and of the neurological sequelae found in well-defined groups of asphyxiated and non-asphyxiated babies.

When relating birth asphyxia to subsequent neurological outcome a fundamental difficulty is the definition of quantifiable indices for the assessment of oxygen deprivation. This has led to a wide variety of definitions of birth asphyxia in several longitudinal studies. The most commonly used methods of assessing the clinical condition of the baby at birth nowadays are the Apgar scoring system and the biochemical markers of oxygen deprivation measured in umbilical-cord blood.

Reviewing literature, the following questions are frequently asked:

- What is the epidemiology and aetiology of "brain damage"?
- What is the pathophysiology of "brain damage" caused by birth asphyxia?
- What is the validity of Apgar scores , umbilical acid-base variables and meconium stained amniotic fluid as specific indices of birth asphyxia and how are they related with early and late neurological findings?
- Does gestational age and/or birth weight influence the incidence of asphyxia and subsequent neurological outcome?

The consequences of birth asphyxia and the difficulties with regard to the definitions will be dealt with in the light of these questions.

## 2.2 Causes of brain damage

Obstetricians and midwives are sometimes blamed when they deliver an infant who has a neurological deficiency or whose subsequent developmental and intellectual performances are below the norm. The assumption is made that the neurological damage is due to obstetric malpractice during the perinatal period.In this context perinatal asphyxia is thought to be the most likely cause of brain damage. The illogic of these assumptions has recently been discussed (Illingworth 1985, Holm 1982). While it is true that fetal asphyxia can cause fetal brain damage, the infrequency of this relationship is stressed. Brain damage is the end result of a wide variety of pathological processes and in most cases cannot be ascribed to a single event at birth.

In this section it will be shown that the causes of brain damage are numerous, and that they interact with each other. The prenatal, perinatal and postnatal risk factors will be reviewed successively with the help of recent literature.

### Prenatal factors

Estimating the incidence of prenatal factors in the causation of brain damage is almost impossible because the factors are very numerous, difficult to identify and often completely unrecognized. In the aetiology of cerebral palsy (CP), O'Reilly & Walentynowicz (1981) found solely prenatal factors in 38.5% of 1503 cases; Holm (1982) found a 50% incidence in 142 cases of CP.

A history of "relative infertility" in the parent (longer than usual delay of conception), or of "reproductive wastage" (abortions, stillborns, neonatal deaths etc.) has been noted in many studies of children with CP. Chefetz (1965), for example, found 78.4% of reproductive insufficiency in 275 cases of CP.

Genetic factors, which are thought to be important in CP, are often not recognized due to the absence of autopsies and chromosal cultures. Illingworth (1958) found genetic factors in 4% of the affected siblings and Treffers et al. (1981) found that more than

20% of the congenital abnormalities involved the nervous system.

Fetal infections, especially those caused by the TORCH agents (toxoplasma, other, rubella virus, cytomegaly virus and herpes simplex virus) were found to be associated with 2% of major congenital malformations. These foetal infections will damage the brain causing up to two more or less severe defects per 1000 live births (Pettay 1979).

Dale & Stanley observed higher incidences of antepartum haemorrage (19.3%) in the mothers of CP children (n=313) compared to control groups (5.3%). This observation is in agreement with those of Chefetz (1965) and Hagberg et al. (1976).

Maternal ingestions, such as drugs (e.g. coumarin derivatives, some anticonvulsant drugs etc.) and toxic substances (smoking, alcohol abuse, mercury and lead poisoning) are particularly likely to affect the nervous system.

Gestational age and birth weight are specially thought to be related to the neurological outcome. Hagberg et al. (1976) found a low birth weight (LBW) in about one third of all children with CP (30% LBW in 200 children with hemiplegia and 41% in children with spastic diplegia). In a more recent study by the same author (Hagberg 1979) term small-for-dates (SFD) infants were observed to have a slightly higher risk of CP than term appropriate-for-dates (AFD) infants, but SFD infants had a much lower risk of CP than premature AFD infants and premature SFD infants. In an excellent review article, Allen (1984) concluded that there is only a slightly increased risk of CP and mental retardation in term SFD infants as compared to AFD infants. She also pointed at the fact that there is an increased risk of all aspects of minimal cerebral dysfunction (speech and language problems, minor neurological abnormalities, attention deficiencies, school failures, etc). in term SFD infants. As mentioned above, Hagberg (1979) found a significantly higher incidence of CP in children who had been preterm SFD infants than in children who had been term SFD infants. Only one study showed a significantly increased risk of CP and/or neurological handicap in premature SFD compared to premature AFD infants (Commey & Fitzhardinge 1979). Several other studies could not confirm this (Koops 1978, Vohr et al. 1979, Saint Anne Dargassies 1977). There is no consensus in literature at all over

the relationship between growth retardation and late sequelae for LBW infants (Touwen & Huisjes 1984).

Very often preterm birth and intra-uterine growth retardation (IUGR) are associated with a variety of pregnancy complications, such as pre-eclampsia, antepartum haemorrhage, placental separation, uterine anomalies, polyhydramnios, etc. These pregnancy complications may lead to maldevelopment or intra-uterine hypoxia and finally to brain damage.

Sigmund Freud (1968) was one of the first to mention that preterm delivery, hypoxia or difficult labour were the result, not the cause, of the conditions which led to CP. Emminger (1956) stated that: "prenatal lesions are the cause of neonatal anoxia which is falsely ascribed to birth trauma." The primary cause of CP, according to this author is "fetal maldevelopment, rendering the fetus liable to suffer severe, generally fatal injury during the actual process of birth." Michaelis et al. (1980) argued that prenatal factors could cause hemiparesis, because natal and postnatal intensive care seemed to be effective in preventing diplegia but not hemi-paresis. The incidence they reported remained constant over the years.

Finally, it can be said that it is unusual to find only one cause for a given case of CP. The importance of a multiplicity of factors, e.g. interrelations between harmful prenatal factors, has been shown by Chefetz (1965) and Touwen (1984).

Perinatal factors

Brain damage can occur during labour but the large majority of children who have experienced severe perinatal hypoxia do not show evidence of brain damage at long-term follow-up (Steiner & Neligan 1975, Scott 1976, Thomson 1977, de Souza & Richards 1978). It is difficult to estimate the percentage of children with CP caused by the process of birth. Cardwell (1956) reported in her book on CP, that the actual birth process accounted for only 5% of the cases.

Relative factors concerning the reversibility of possible damage must include the severity and duration of hypoxic insults in the perinatal period. Complete recovery is far more likely after an episode of complete anoxia during delivery than after repeated or prolonged anoxia in the prenatal period (Myers 1972). Prenatal

factors which may cause chronic intra-uterine hypoxia and subsequent brain damage must also be considered. These prenatal lesions may be the cause of neonatal anoxia, falsely ascribed to birth trauma. The significance of asphyxia present at birth in relation to neonatal neurological morbidity is the main subject of this thesis and will be extensively evaluated in the next chapters.

Postnatal factors

A much closer relationship was found between neonatal predictors (severe RDS, seizures) and late sequelae (Peacock & Hirata 1981), than between delivery factors and late sequelae. The same was found by Touwen et al. (1980) for the neonatal neurological condition. The neonatal management of hypoxia, respiratory distress syndrome (RDS), hypoglycaemia, hypothermia, intra-vertricular haemorrhage (IVH) and convulsions especially in very low birth weight (VLBW) infants may by itself cause the brain damage or aggravate the effects of pre- or perinatal factors. For instance, mechanical ventilation was associated with a high incidence of neurodevelopmental sequelae (Rothberg et al. 1981). Acute intra-cranial haemorrhage was found to be the major neurological complication of the VLBW infant (Volpe 1981) and the degree of haemorrhage, according to the gradation of Papile et al. (1978) had a direct relationship to mortality and long-term morbidity (Thorburn et al. 1981).

Unknown aetiology

Paine (1968) found no plausible aetiological factors for 30% of the cases of CP in the 1100 children he investigated. This percentage is in agreement with other studies (Holm 1982, Durkin et al. 1976). Illingworth (1985) analysed four representative reports of 1392 cases of mental subnormality without CP and found that 840 (60%) were of unknown aetiology.

From the above it can be concluded that the aetiology of "brain damage" is much more complicated than would be suggested by the information from the media over the "blue looking" baby at birth. There is a clear overestimation of the rate of handicap after asphyxia at birth has occurred (Paneth & Fox 1983).

## 2.3. Birth asphyxia and brain damage

The hypoxic-ischaemic lesions caused by asphyxia (see general introduction) involve almost all organ systems; however, neurological sequelae have the most longterm effects. Most studies on pathophysiological events in the fetal/neonatal brain following birth asphyxia (Brann & Dykes 1977, Woods 1983, Kreusser & Volpe 1984) mention the fact that the final oxygen supply of the fetal brain depends on the oxygen content of the blood and the amount of blood flow to the brain. The aetiology of cellular damage in the CNS of the asphyxiated fetus remains controversial. A considerable variety of neuropathological features of "neonatal hypoxic-ischaemic encephalopathy" can be seen. Clinical-neuropathological studies of patients who had sustained "asphyxial" insults to the CNS showed that the type of cerebral damage in the preterm infant is different from that seen in the full-term infant (Towbin 1970). In the preterm infant the damage is located in the periventricular region (germinal matrix). In the full-term infant it is found in the grey substance of the cerebral cortex.

Brann & Dykes (1977) proposed the following features of the effect of intra-uterine (IU) asphyxia on the CNS of the full-term newborn. After a prolonged period of IU asphyxia the full-term infant can have very low Apgar scores at birth, with or without evidence of shock. The clinical course after birth depends on the multiplicity of organ systems affected. Sexon et al. (1976) followed 53 infants that needed resuscitation after IU asphyxia. 18 infants had no clinically significant diseases. Nine of the 53 infants died during the neonatal period. The most common cause of death was malignant hypoxia from "persisting transitional circulation". Only two infants died from CNS disturbances. In the 35 infants with clinical diseases the affected organ systems were (in order of decreasing frequency): the pulmonary system, the cardiovascular system, the CNS, the gastrointestinal tract and the renal system. In 19 infants more than one system was involved. No single system appeared to be the primary target of asphyxia. Only one third of the infants showed clinical signs that suggested CNS involvement. These are fairly characteristic and include seizures,

an abnormal state of consciousness, an abnormal respiratory pattern, abnormal posture, abnormal tone etc.

In conclusion, fetal hypoxia may result in cerebral ischaemia and cellular hypoxia leading to necrosis and possible CNS handicap if the child survives. The pathological changes in the brain of a fullterm or preterm infant, who has experienced an episode of IU asphyxia, depend on the characteristics of the affected fetus (i.e. gestational age, birth weight), the degree and duration of the asphyxial episode and on the length of survival of the patient .

Proposed pathogenesis (historical review)

Little (1862) already mentioned the association of "abnormal parturition, difficult labour and asphyxia neonatorum" with cerebral palsy in 1862. Since that time significant observations have led to the present understanding of brain damage originating in the perinatal period. Clifford (1941) showed specific effects of perinatal asphyxia on the brain of infants who died in the neonatal period after being delivered by Caesarean section because of premature separation of the placenta. The particular pathological findings were swelling of the brain and cerebral necrosis. Although the general observations were extremely important in establishing the relationship between asphyxia and cerebral damage, the relative role played by asphyxia remained a subject of speculation until data from specific animal models appeared.

Ranch & Windle (1959) studied the effects of acute total asphyxia on the nervous system of the newborn monkey. These effects were thought to be comparable to the human setting. Swelling of the brain and cortical necrosis was not found in surviving monkeys, even though the length of asphyxia was long enough to produce damage to the brain stem, thalamus, basal ganglia and spinal cord. It was obvious that neither the clinical course nor the pattern of CNS damage resembled that which was most frequently found in human infants after perinatal asphyxia. The injury pattern of the brain stem was rarely seen in the human infant. The animal model giving more insight into the pathogenesis of perinatal brain damage was the monkey model of IU partial asphyxia (Brann & Myers 1975). After a three to four hour period of partial asphyxia, brain swelling and

cortical necrosis were found at necropsy after four days of life. A typical finding of ulegyria dependent on the degree and localization of cerebral necrosis was found after six months of life. This damage to the cerebral hemispheres is a pathological picture similar to that observed in humans with cerebral palsy.

On the basis of these available human and animal data the following pathogenesis was proposed for most perinatal hypoxic-ischaemic brain damage in full-term newborn infants (Brann & Dykes 1977). After a certain period of IU asphyxia an increase in perfusion of the brain and the heart occurs, with a decrease in kidney, placenta and lung perfusion. This happens in order to maintain a continuous supply of oxygen and glucose to the CNS and heart muscle. After some time tissue oxygen levels decrease gradually, also in the CNS and heart. The neurons of the cortex and basal ganglia are the most dependent on oxygen, whereas neurons in the brain stem, spinal cord etc. are able to withstand longer periods of oxygen deprivation. As the oxygen deprivation in the tissues increases shifts occur in the distribution of electrolytes and an increase in the water content of the brain develops. Total cerebral vasomotor paralysis and reduction of cerebral blood flow occur due to local tissue acidosis. Focal areas of ischaemia lead to generalized brain swelling and thereafter to an increase in intra-cranial pressure. Irregular respiration and apnoea develop and lead to death in the neonatal period.

Kreusser & Volpe (1984) recently reviewed the distinct neuropathological varieties of neonatal hypoxic-ischaemic encephalopathy. Brain swelling and especially selective neuronal necrosis are the most common varieties of injury observed in full-term infants. Sites of predilection for selective neuronal necrosis are numerous and widespread. Neurons of the cerebral cortex are particularly vulnerable (hippocampus, visual cortex, motor and sensory cortices). Furthermore, lesions in the basal ganglia (status marmoratus) and parasagittal cerebral injury are characteristic findings especially in full-term infants. Periventricular leukomalacia (necrosis of the white matter adjacent to the lateral ventricle) is most often observed in preterm infants. Finally, focal and multifocal ischaemic brain necrosis (necrosis within the specific distribution of major cerebral

vessels) are often seen, which can be associated with dissolution of brain substance and the formation of cavities (porencephaly and hydranencephaly).

Besides the usual assumption that diminished brain perfusion was the primary cause of brain swelling, Myers (1979) recently suggested an alternative explanation. In his metabolic studies on monkeys he found that all animals with brain swelling had high concentrations of lactate in the cerebral cortex. He observed no differences in the $pO_2$ and pH between animals which recovered and those which developed asphyxial brain damage. The crucial differences between the two outcomes were 1) lactate content of the blood and cerebrospinal fluid and 2) a fall in mean arterial blood pressure below a critical level. Therefore, for brain damage to occur in an asphyxiated fetus the lactate level in the brain must reach a critical level ( 20 umol/g) and this critical level is only reached if the tissue acidosis induced by asphyxia is aggravated by a severe drop in the mean arterial blood pressure. Myers (1977) also noted that brain damage in the surviving monkey neonate was rare. He reported that virtually all asphyxiated monkey fetuses either succombed in utero or survived to be neurologically normal. Myers was only rarely able to produce the desired brain damage in the surviving monkey neonate. Many authors using clinical human populations reported a similar all-or-none effect of hypoxia on the surviving human infant (Niswander 1979). These human "experiments" are, of course, not as well controlled as the laboratory exercises since neither the degree of asphyxia nor the $O_2$ saturation and lactate levels in fetal blood can be measured with precision in the clinical patient.

## 2.4. The Apgar scoring system

The Apgar scoring system (Apgar 1953) is the traditional and most universally used system for the assessment of the newborn infant's condition in the delivery room. Virginia Apgar, an anesthesiologist, was interested in establishing the effect of anesthesia and analgesia on the fetus and also in identifying infants requiring resuscitation after birth. She designed a score that assesses five categories of functions necessary to sustain

life (heart rate, respiratory effort, muscle tone, reflex irritability and skin colour). Each of the categories are rated 0, 1 or 2 and are added. Without doubt, the Apgar score has its merits and Apgar's work (1962) has demonstrated clearly that the one-minute Apgar score is a useful predictor of neonatal mortality and the five-minute score is a useful predictor of neonatal morbidity.

The predictive power ofthe Apgar score is limited to the immediate future. It only gives a direct clinical impression of whether the infant's condition is satisfactory ($\geq 7$), severely depressed ($\leq 3$) or in between. As the scoring is only done when necessary in the first 15 to 20 minutes, it basically measures the immediate capacity of the neonate for an alarm reaction. The kind and depth of depression which may follow later and which represent the depleted resources of the baby is in no way predicted by the Apgar score and this is one of the reasons why the Apgar score has been a disappointment to paediatricians and paediatric neurologists. Furthermore, the Apgar scoring system is subject to a wide inter-observer variability. Sometimes the scoring is done retrospectively as part of the necessary paperwork and certainly not measured at exactly one, three and five minutes after birth.

The Apgar score is used as the index of birth asphyxia because asphyxia is thought to be an important and perhaps the most common potential contributor to depression of the newborn infant. Recently, however, correspondents have become more critical of the application of the Apgar score as an established indicator of asphyxia (Lancet letters 1982). In addition to asphyxia many other factors, including depression of respiratory centres by anesthesia or intra-cranial injury etc., may result in a clinically depressed neonate as signalled by low Apgar scores. In these cases other signs of asphyxia, such as hypoxia or $CO_2$ retention, are not present as long as oxygenation is maintained by artificial means.

### 2.4.1. Relationship between Apgar scores and the neonatal neurological condition

Until now there are very few studies available on the relationship between Apgar scores and neonatal neurological

condition. Brown et al. (1974) found that 80% of the infants with a very low Apgar score (0-3 at one minute) showed behavioural abnormalities in the neonatal period. These included feeding difficulties, apnoeic or cyanotic attacks, apathy, convulsions, hypothermia, a "cerebral cry" or persistant vomiting. From figures presented by Litschgi et al. (1974) it can be calculated that neonatal neurological abnormalities were found in approximately one quarter of the infants with a low one-minute Apgar score (<7) and in one half of the infants with a low five-minute Apgar score, compared to 5% in infants with normal Apgar scores. It must be emphasized that in this study approximately 40% of the neurologically abnormal infants were born preterm. Prematurity is associated with a high incidence of neonatal neurological abnormalities (Huisjes et al. 1980) and a higher percentage of low Apgar scores (Goldenberg et al. 1984). The two-minute Apgar score was found to be of little value in predicting neonatal non-optimality (using Prechtl's neurological examination technique) in a relatively small group of 133 infants (de Jong thesis 1975).

### 2.4.2. Relationship between Apgar scores and the neurological condition in later life

Drage et al. (1964 and 1966) confirmed the findings of Apgar, i.e. that neonatal mortality is best predicted by the one-minute Apgar score and that the five-minute Apgar score is best used to predict infant morbidity (Table 1). According to Drage et al.

Table 1. Percentage of neurologically abnormal children at one year of age in relation to Apgar scores

| Apgar score | 1 minute % | 5 minute % | 5 minute score by birth weight (g) 0-2000 | 2001-2500 | ≥ 2501 |
|---|---|---|---|---|---|
| 0-3 | 3.6 | 7.4 | 23.5 | 12.5 | 4.3 |
| 4-6 | 2.8 | 5.3 | 14.5 | 4.6 | 4.2 |
| 7-10 | 1.6 | 1.7 | 8.8 | 4.0 | 1.4 |
| TOTAL | 1.9 | 1.9 | 10.8 | 4.1 | 1.5 |

(Drage et al. 1966 - modified)

(1966) it was impossible to know whether low one and five minute Apgar scores were signs of already neurologically abnormal children at birth or whether the pathological mechanisms (e.g. asphyxia) underlying low Apgar scores were responsible for the neurological impairment detected at one year of age. Even if it is assumed that low scores always reflect severe asphyxia, Drage's data show clearly that this effect of asphyxia varies considerably within different birth weight groups (Table 1). His findings suggest that low Apgar scores are more hazardous (increased percentage of neurologically abnormal infants) in the lower birth weight group than in the higher birth weight group. Dweck et al. (1974) subjected 15 infants who were asphyxiated at birth (one-minute Apgar score 0-3 and requiring positive pressure oxygen by endotracheal tube) to a neurological examination between the ages of 15 to 40 months. Ten were found to be neurologically normal, two had borderline results and three showed evidence of neurological deficiencies; the latter were IUGR babies. The data of Dweck et al. (1974) suggest that in the absence of chronic intra-uterine compromise the prognosis after profound perinatal asphyxia, which is aggressively managed with current techniques, is excellent. Nelson & Broman (1977) compared several perinatal chacteristics of 50 children with marked neurological abnormalities with a large (n=34423) neurologically normal control group. 33% of the severely handicapped group (n=16) had a one-minute Apgar score of 0-3, compared to 5% in the control group; at five minutes these figures were 22% (n=10) and 1% respectively.

In 1981 Nelson & Ellenberg stated that the duration of a low score must be taken into account when assessing the severity of asphyxia. The longer a low score persists after birth the higher the incidence of neurological sequelae (Table 2). In low birth weight infants (≤2500g) with very low late Apgar scores the

Table 2. Outcome with latest very low Apgar score (0-3)

| time of latest very low AS (min) | ≤ 2500g live born n | ≤ 2500g death in first year (%) | ≤ 2500g alive with cerebral palsy (%) | >2500g live born n | >2500g death in first year (%) | >2500g alive with cerebral palsy (%) |
|---|---|---|---|---|---|---|
| 1 | 428 | 25.5 | 1.9 | 1729 | 3.1 | 0.7 |
| 5 | 163 | 55.2 | 7.1 | 286 | 7.7 | 0.9 |
| 10 | 67 | 67.2 | 6.7 | 66 | 18.2 | 4.7 |
| 15 | 51 | 84.3 | 0 | 23 | 47.8 | 9.1 |
| 20 | 139 | 95.7 | 0 | 39 | 59.0 | 57.1 |

(Nelson & Ellenberg 1981 - modified)

percentages of cerebral palsy (CP) in the survivors (3.4%) were almost the same as those of normal birth weight infants (>2500g) (0.7%), but in the former group 86% of the infants with very low late Apgar scores died in the neonatal period as compared to 36% in the latter group. A rather long duration of asphyxia is required to produce recognizable brain damage in infants who survive. Of the 385 children with very low late Apgar scores (0-3 at ten minutes or later) almost 70% (n=267) died; of the 30% (n=98) who reached seven years of age 80% were free from major handicap. Apparently survival with brain damage due to asphyxia is relatively uncommon and sudden death or (apparent) intact survival are much more likely outcomes of IU asphyxia. Using one and five-minute Apgar scores as a prediction for the outcome (see NCPP studies - the American Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke), one has to bear in mind that the absolute rate of handicap is low. Another important aspect, also noted by Nelson, is that the quantifications provided by these NCPP studies are relative to specific forms of nursery management between 1959 to 1966. Important aspects in newborn care have subsequently been altered and these data may well be unduly pessimistic for the present day.

2.4.3. What is the risk of death or handicap for the baby with very severe birth asphyxia ("baby born dead")?

Hilary Scott (1976) examined 33 children in whom respiration had not been established within 20 minutes after birth, and whose Apgar score was 1 or 2 at one minute. Sixteen of these 33 babies survived the first month and five, two of whom were severely handicapped, showed signs of cerebral palsy at follow-up. From the 15 infants with a one-minute Apgar score of 0, eight died but six of the seven survivors were normal when examined three to seven years later.

Steiner & Neligan (1975) reported that quadriplegia or deafness manifested itself in later childhood in one baby from a group of 14 with a history of cardiac arrest of five minutes duration and in four babies from a group of 12 with a history of cardiac arrest of more than five minutes duration. De Souza & Richards (1978) performed a follow-up study on 53 term babies with a history of fetal distress (ctg abnormalities, a one-minute Apgar score of 1 or 2 and severe neurological abnormalities in the early neonatal period). In later childhood 78% showed no neurological abnormalities at follow-up, 14% had slight or doubtful abnormalities, 6% showed definite abnormalities but no major handicap and only one (2%) was severely handicapped. Dweck et al. (1974) reported that the severely asphyxiated babies did not differ from control group children without signs of asphyxia as regards IQ or minor neurological abnormalities once the severely handicapped survivors were excluded from the analysis.

In the NCPP study 87 children survived severe, prolonged asphyxia without manifestation of cerebral palsy (Nelson & Ellenberg 1981). Six of these children had speech defects and two were deaf. The incidence of a visual defect, mental retardation and hyperactivity did not differ from those found in the whole of the NCPP study.

From all these studies it can be concluded that severe asphyxia is associated with a high mortality rate (about 50%), and that the prognosis for surviving babies is better than had been thought.

## 2.5. Fetal and maternal acid-base physiology

Fetal and neonatal blood gas and pH measurements have the last decade extensively been used mainly for diagnostic purposes but also to evaluate perinatal care.
In obstetrics, the interpretation of blood gas and pH measurements, however, is a complex subject, because 1) a single determination is only a "snapshot" in a dynamic process and repeated sampling is therefore often necessary, 2) fetal acid-base "homeostasis" is partly dependent on that of the mother, with the consequence that simultaneous analysis of both maternal and fetal pH and blood gases is sometimes essential, 3) a wide range of "normal" values is found in different studies and 4) often only pH values have been determined making it unclear what kind of acidosis (respiratory and/or metabolic) one is dealing with.
In this part of Chapter 3 some aspects of fetal and maternal acid-base physiology and their interrelationships during normal pregnancy and delivery are given. Some remarks on the validity of and some methodological aspects on fetal and umbilical acid-base determinations, as indicators of hypoxia/asphyxia, will be given.

### 2.5.1. Fetal blood gas and acid-base physiology

The chief organ of the acid-base "homeostasis" in the fetus is the placenta which, in this respect, has the function of lungs, gastrointestinal tract and kidneys.
The fetus obtains its $O_2$ by transplacental diffusion from the mother to the fetus. The higher fetal hemoglobin (Hb) concentration than that of the mother and the greater affinity for $O_2$ of fetal Hb influence this transport of $O_2$ across the placenta. The fetus rapidly disposes $CO_2$ across the placenta by diffusion in maternal blood. Noncarbonic (fixed or nonvolatile) acid is the waste product of anaerobic metabolism. To compensate for an anaerobic induced lactic acid acidosis fetal buffers are used. The two main fetal buffer systems are bicarbonate/$CO_2$ and hemoglobin. Utilising these buffers results in a decrease in total buffer capacity and fetal pH falls, $pCO_2$ increases and a mixed acidosis develops. Since Base Excess (BE) quantitatively reflects the measure of

a metabolic acidosis, even in cases of mixed acidosis, it proved to be of great value in obstetrics. BE can be determined from nomogram calculations following measurements of pH, $pCO_2$ and haematocrit values (Siggaard-Anderson 1963) and these calculations, originally constructed for adult blood, seem to be applicable to fetal blood (Rooth & Thalme 1970).

### 2.5.2. Maternal and fetal acid-base relations during pregnancy and delivery

Normally the mother is overbreathing (hyperventilating) in late pregnancy causing a hypocapnia and a renal compensated respiratory alkalosis. The fall in maternal $pCO_2$ favours the transport of $CO_2$ from fetal blood across the placenta (Hytten & Chamberlain 1980).
Fetal scalp blood sampling at the beginning of labour, introduced by Saling (1962), created the possibility of assessing the fetal condition more directly by biochemical measurements. At that stage, fetal blood is found to be more acid than maternal blood (0.1 pH unit lower; Table 3). Recently techniques were introduced into clinical practice for obtaining samples of fetal blood in the umbilical cord by fetoscopy (Mackenzie et al. 1984; Soothill et al. 1986) and by direct puncture of the vessels through the anterior abdominal wall. These techniques will provide us a greater understanding of fetal acid-base physiology in the near future.

Table 3. Normal blood gas and acid-base values in the mother, fetus and newborn during pregnancy, labour and in the immediate postpartum period

| | MATERNAL | | FETAL | | UMBILICAL | | | MATERNAL |
|---|---|---|---|---|---|---|---|---|
| | late pregnancy arterial (P) | early labour venous (T) | early labour scalp (R) | second stage (R) | artery ($S_x$) | (D) | (E) | after birth venous (D) |
| pH | 7.40 | 7.43 | 7.37 | 7.30 | 7.20 | 7.21 | 7.24 | 7.34 |
| $pCO_2$ (kPa) | 4.5 | | 5.1 | 5.7 | | 6.9 | 6.0 | |
| BE (meq/l) | -4 | -3 | -3 | -5 | -8 | -5 | -7 | -5 |

Data tabulated from the following references: Rooth et al. 1972 (R); Parer 1980a (P); Sykes et al. 1982 ($S_x$); Eskes et al. 1983 (E) and Dijxhoorn 1986 (D).

Unlike the relative stable state of pregnancy, labour is a dynamic process resulting in progressive changes in maternal and fetal acid-base values. During the second stage of labour a mild maternal acidosis develops. The pH falls about 0.1 unit and the BE decreases by 2 to 3 meq/l, indicating that the acidosis is metabolic in nature. This maternal metabolic acidosis has been attributed to stress, increased muscular activity of labour and relative starvation leading to accumulation of lactic, keto etc. acids and is more profound in prolonged and difficult labour and in nulliparas as compared to multiparas (Jacobson et al. 1970). Because of different management of labour changes in maternal- as well as fetal acid-base status may differ from one center to another (Rooth et al. 1973). Fetal pH remains virtually unchanged during the first stage of labour, but usually during the second stage it will decrease (Table 3).

Besides the fact that the decrease in fetal pH can be caused by diminished transplacental diffusion of $O_2$ and $CO_2$, it is thought to be caused by organic acids crossing over to the fetus of an acidotic mother (infusion acidosis). Several authors reported transfer across the human placenta of bicarbonate (Newman et al. 1967; Caspi et al. 1966), lactate (Daniel et al. 1966) and/or ammonium chloride (Newman et al. 1967) and after a lag period of several hours (two to four hours) a maternal metabolic acidosis was accompanied by a fetal acidosis. The exact mechanism for buffer anions and organic acids to cross the haemochorial placenta, however, is not known (Kastendieck & Moll 1977). However, Blechner et al. (1967) and more recently Aarnoudse et al. (1984) with their in-vitro placental perfusion experiments, showed a minimal placental permeability for $H^+$ and bicarbonate ions, indicating a protection of the fetus against a maternal acidosis. The latter study showed evidence of a placental bicarbonate pool which may protect the fetus against changes in maternal pH and blood gas status by acting as an additional buffer between the two circulations. Furtheron, it has been shown that lactate can be produced in the human placenta (Illsley et al. 1984). Whether lactic acid in the maternal circulation is exchanged against bicarbonate from the fetal circulation, or vice versa, remains a question.

Because of evential transmission of buffer anions or corresponding fixed organic acids, several authors (Beard et al. 1966; Rooth et al. 1973) recommended to take the maternal acid-base state into account when

assessing the origin of a fetal pH decrease. They introduced delta pH (Δ pH) and delta BE (Δ BE) as additional acid-base parameters, indicating respectively differences between maternal venous pH or BE and fetal pH or BE. That Δ pH values are not always valuable will be discussed in Chapter 4. Δ BE was introduced because it should offer a more practical method of discriminating between a fetal hypoxic acidosis and a maternal infusion acidosis. An increase in Δ BE will indicate the former situation and a decrease the latter.

### 2.5.3. Validity and reliability of fetal/umbilical acid-base parameters

Are fetal blood and umbilical cord blood gas sampling valid techniques for determining fetal and immediate neonatal acid-base status and are these determination reliable indicators of fetal or neonatal asphyxia/ hypoxia?

The validity is strongly dependent on the correct interpretation of the obtained measures and therefore some important factors have to be taken into account.

- Transient versus permanent and chronic versus acute asphyxial events. With single pH, blood gas and acid-base determinations neither the duration nor the severity of a preceeding insult can be revealed. Repeated sampling is in many cases obligatory
- Type of the acidosis (respiratory or metabolic), which will be discussed in the section "asphyxia"
- Relationship to maternal pH and BE, as disturbances in fetal acid-base status may mirror in fact the maternal state and is not an indication of an intrinsic fetal endogenous acidosis
- Stage of labour, whereas abnormalities in laboratory values are of far greater significance in the early first stage of labour than in the late second stage.

Concerning the reliability of fetal blood gas and acid-base parameters some important remarks should be made.

- Direct measurement of scalp $pO_2$ has been shown to has its restrictions due to scalp blood flow reduction in the course of labour (tonsure effect - O'Connor et al. 1979; Smits & Aarnoudse 1984) and the Bohr effect. As the $O_2$ dissociation curve in the fetus is steeper than in the adult, a small change in fetal $pO_2$ leads to a large change in $SO_2$. With fetal acidosis measurements of fetal $pO_2$ alone may lead to a false

impression of the state of oxygenation of fetal blood, since $pO_2$ may be relatively high despite low $SO_2$ values. Thus, $SO_2$ will provide more useful information about the oxygenation of fetal blood than $pO_2$. However, until now no valuable measuring technique for fetal $SO_2$ is available.

- Fetal pH values can be influenced by a quick (acute) process, which is reflected in changes of $pO_2$, $pCO_2$ as well as $SO_2$, but it can also be a measure of the consequence of hypoxaemia which is reflected in more or less slow (chronic) metabolic changes (BE and lactate)
- Fetal acidosis is not always the result of hypoxaemia. For instance, changes in fetal pH secondary to maternal acidosis or alkalosis may lead to false low or false high fetal pH values. In these circumstances one can better use $\Delta$pH and $\Delta$BE values.

### 2.5.4. Methodological aspects of fetal/neonatal blood gas and acid-base assessment

Errors in technique of sampling may lead to a false assessment of the fetal or newborn acid-base status. Presence of a caput succedaneum, amniotic fluid contamination, delayed analysis etc. may lead to false low pH values and plastic tubing, exposure to air etc. to false high fetal pH values. When for practical reasons a delay between sampling and analysis exists, the results will change over time. Although Schurz et al. (1976) showed relatively constant gas values within 1½ hour after storage on ice, Nhan et al. (1980) observed a mean total pH decrease in the umbilical vein of 0.064 units over 24 hours, i.e. 0.003 unit/hour. Analysis as soon as possible after the samples are obtained is mandatory, especially to prevent glycolysis in the white blood cells (Astrup et al. 1960). Adding fluoride (NaF) to the samples seems to be adequate to limit changes during storage on ice (Nhan et al. 1980). Adding heparine to the samples will decrease the pH considerably, especially when more than 0.1 cc of heparin is used. To obtain the most reliable estimations of pH one should puncture the cord as soon as possible after birth and test them within 30 minutes. Standardization of the interval between delivery and cord clamping is very important (Pel & Treffers 1984). Also late versus early clamping of the cord should be considered, as several studies (Schurz et al. 1974; Pel & Treffers 1984) showed a significant decrease of umbilical pH values in the first minutes

of extrauterine life.

## 2.6. Asphyxia and the fetal/newborn acid-base status

In terms of acid-base values asphyxia can be defined as depletion of $O_2$ and accumulation of $CO_2$, leading to a state of acidosis which during intrauterine life is due to interference with placental gaseous exchange (Towell et al. 1976).

Studies on animal fetuses and newborns have contributed significantly to our understanding of the body's metabolic response to asphyxia and hypoxia. James et al. (1963) investigated the effect of total asphyxia/anoxia in newborn puppies and demonstrated that the $SO_2$ fell from 90% to less than 10% in two minutes. $CO_2$ accumulated (0.7-1.3 kPa/min), buffer base fell (2 meq/l/min) and pH fell (0.1 unit every three minutes). Total anoxia in human, as seen with abruptio placentae totalis or prolapse of the cord, is rare. Asphyxia in the human fetus is usually the result of partial $O_2$ deprivation and $CO_2$ accumulation.

The "chronically" instrumented fetal sheep provides a convenient model for examining the acid-base changes in response to various types of hypoxia, especially with regard to the severity and the duration of hypoxia. In studies, in which acute fetal hypoxaemia was produced by maternal hypoxia (Cohn et al. 1974; Parer 1980) essentially no change in fetal $pCO_2$, but a gradually developing metabolic acidosis was observed. Reducing uteroplacental (Cohn et al. 1985) or umbilical perfusion (Itskovitz et al. 1983), however, resulted also in hypercapnia. In the chronic experimental growth retarded fetal sheep (Robinson et al. 1985) chronic hypoxaemia and hypoglycaemia without acidaemia was found.

In the human fetus, especially in the severily intrauterine growth retarded one, it also seems reasonable to assume that chronic hypoxaemia might be present in utero. Bekedam & Visser (1984) showed evidence that recurrent "late" FHR decelerations may signal these hypoxaemic episodes. At birth, Aarnoudse (1984) observed lower umbilical venous $pO_2$ and pH values and Lin et al. (1980) lacticemia of more severity in growth retarded infants than in appropriate-for-dates infants. The question whether these low $pO_2$ values and acidaemia were already present antenatally, could in these studies not be answered.

In order to recognize the type and severity of a fetal acidosis, Lumley

& Woods (1973; Table 4) described limits of the normal range for pH and blood gases in fetal scalp blood during labour and three types of

Table 4. The boundaries of the normal range (inventory of 14 different studies by Lumley et al. 1971) and normal values (Lumley & Wood 1973) of fetal scalp blood gas and acid-base values.

| | FETAL SCALP | | |
|---|---|---|---|
| | lower limits | upper limits | normal values |
| pH | 7.15- 7.30 | 7.33- 7.47 | > 7.25 |
| $pCO_2$ (kPa) | 2.9 - 4.5 | 6.7 - 8.9 | < 8.0 |
| $pO_2$ (kPa) | 0.9 - 2.3 | 3.1 - 4.8 | > 2.3 |
| BE (meq/l) | -14.1 - -5.3 | -4.3 - +3.0 | > -8.0 |

acidosis. 1) A respiratory (or hypercapnic) acidosis (pH <7.20, $pCO_2$ >8.0 kPa and normal BE); 2) a metabolic acidosis (pH <7.20, normal range $pCO_2$ and BE< -9 meq/l) and 3) a mixed respiratory-metabolic acidosis (pH < 7.20, $pCO_2$ > 8.0 kPa and BE< -9 meq/l).

To get more insight into abnormal umbilical artery blood gas and acid-base values, the lowest centiles (c10, c5 and c2.3) of $pH_{ua}$ and $BE_{ua}$ values and the highest centiles (c90, c95 and c97.7) of $pCO_{2ua}$ values in three big study cohorts from different centers are given in Table 5. Sykes et al. (1982) defined a severe acidosis as a $pH_{ua} \leq 7.10$ ( > 1 SD

Table 5. Centiles of pH, $pCO_2$ and BE out of the umbilical artery in three different centers: Sykes et al. (S) (1982; n = 899), Eskes et al. (E) (1983; n = 4667) and Dijxhoorn (D) (1986; n = 2220).

| | $pH_{ua}$ | | | $pCO_{2ua}$ | | | $BE_{ua}$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | (S) | (E) | (D) | (S) | (E) | (D) | (S) | (E) | (D) |
| c2.3 | | 7.06 | 7.00 | | | | | -16 | -16 |
| 2 SD from mean | 7.04 | | | | | | -17 | | |
| c5 | | 7.10 | 7.05 | | | | | -14 | -14 |
| c10 | | 7.14 | 7.09 | | | | | -13 | -11 |
| 1 SD from mean | 7.10 | | | | | | -12 | | |
| c50 | 7.20 | 7.24 | 7.21 | | 6.0 | 6.9 | - 8 | - 7 | - 5 |
| c90 | | | | | 7.7 | 8.9 | | | |
| c95 | | | | | 8.4 | 9.6 | | | |
| c97.7 | | | | | 9.1 | 10.3 | | | |

below the mean) and a base defecit > 13 meq/l ( >1 SD above the mean) and very severe acidosis as a $pH_{ua}$ <7.04 ( >2 SD below the mean) and a base defecit >17 meq/l ( > 2 SD above the mean). This data is consistent with our presented below the c10 and below the 2.3 values respectively (Table 5).

To exclude the possible influences of maternal changes on fetal acid-base status, also Δ pH and Δ BE may give an indication of the severity of fetal asphyxia. Khazin & Hon (1971) found a good correlation between the increase in Δ pH and the severity of abnormal FHR patterns. Rooth et al. (1973) observed that the fetal $pO_2$ significantly decreased when the Δ pH increased and they suggested that when the fetal pH was more than 0.20 pH units below that of maternal venous blood, errors of pH interpretation by maternal infusion acidosis would be minimised.

From this section "Physiology and pathology of the fetal/newborn acid-base status" it can in conclusion be said that, determinations of fetal pH values alone give insufficient information about the severity and the duration of hypoxia/asphyxia. Therefore, besides maternal and fetal pH values, also blood gas and acid-base values have to taken into account.

## 2.7. Relationship between umbilical cord acid-base values and neurological outcome

It is generally accepted in literature that brain damage can be the consequence of fetal hypoxia. The Human Concensus Development Task Force (Zuspan et al. 1979) therefore recommended further research to establish the magnitude of the contribution of intra-partum hypoxia to the spectrum of short and long-term neurological sequelae.

The extent to which the biochemical indicators of hypoxia (e.g. acidaemia and decrease of buffer base values measured at birth by acid-base assessment from the umbilical cord) are reliable predictors of damage to the nervous system will now be reviewed.

### 2.7.1. Relationship between umbilical cord acid-base values and neonatal neurological condition

Litschgi et al. (1974) showed that low umbilical artery pH ($pH_{ua}$) values (<7.09) in a total group including a high percentage of preterm infants corresponded with an increased incidence of pathological neonatal neurological consequences (30% had abnormalities). In a group of 122 asphyxiated infants (buffer base < 36.1 meq/l) of whom 18% were preterm and 20% were growth retarded, Low et al. (1977) demonstrated the trend that severe neonatal cerebral symptoms are associated with more severe metabolic acidosis at birth. However, the mean $pH_{ua}$ values in infants with cerebral symptoms were not different from the values of asphyxiated infants with no cerebral symptoms. Low suggested that the relatively short duration and complete resolution of these symptoms was an expression of the reversibility of cerebral insults. It is possible that a sublethal insult may indeed produce brain damage and the neonate may appear "abnormal or suspect" during the perinatal period but clinical recovery may occur in subsequent days, weeks or months (Niswander et al. 1975). The outcome of severe intra-uterine metabolic acidosis in humans, as well as in animals, might be an all or nothing effect (Niswander 1975 and 1979), i.e. fetal or neonatal death or no damage at all. Such an explanation is supported by findings in the monkey experiments of

Myers (1972 and 1977).

Several studies in the Netherlands have used the neonatal neurological examination technique described by Prechtl (1977) to assess relationships between umbilical cord pH values and neonatal neurological condition. Stolte et al. (1980) demonstrated that the pH values of the umbilical arterial blood of infants born in the vertex position (n=75) correlated with a score of neurological optimality, based on a representative list of neonatal neurological examination items of the neonate. A pH value of more than 7.25 was nearly always associated with neurological optimality and pH values of 7.25 or less were practically equally divided over optimals and non-optimals. In breech born infants (n=48) such a relationship could not be demonstrated by the same group of authors (de Jong 1982). Lievaart & de Jong (1982) found that in a group of 85 infants delivered by midwives, ten neurologically non-optimal neonates (i.e. with a score lower than 37 or a total of 42 neurological non-optimal items) had significantly lower pH and base deficiency values than the 75 neurologically optimal neonates. No neurologically non-optimal infants were found in a small number of infants delivered by gynaecologists (n=27). The $pH_{ua}$ at birth was kept above 7.20 at the expense of a high percentage of operative deliveries. In a much larger study group (n=2303) the risk of neonatal neurological abnormality in appropriate-for-dates (AFD) full-term infants (Table 6) did not seem to be significantly elevated by acidaemia (Huisjes et al. 1980).

Table 6. Neurological abnormality in relation to acidaemia and intrauterine growth retardation in fullterm and preterm infants

| | fullterm | | preterm | |
|---|---|---|---|---|
| | normal n | abnormal n (%) | normal n | abnormal n (%) |
| AFD, not acidaemic | 1962 | 68 (3.3) | 85 | 11 (11.5) |
| AFD, acidaemic | 258 | 15 (5.5) | 10 | 4 (28.5) |
| SFD, not acidaemic | 251 | 24 (8.7) | 18 | 5 (21.7) |
| SFD, acidaemic | 51 | 7 (12.1) | 12 | 3 (20.0) |

(Huisjes et al. 1980 - modified)

From most of the studies mentioned above, it has become clear that full-term and pre-term small-for-dates (SFD) and appropriate-

for-dates (AFD) infants have to be clearly distinguished as far as the selection of a "high risk" population is concerned. Maturity is the most potent factor influencing the incidence of asphyxia (Low et al. 1977, Huisjes et al. 1980, Westgren et al. 1982). The prognosis is especially poor as regards the neonatal neurological condition for prematurity combined with acidosis (Litschgi et al. 1974, Huisjes et al. 1980, table 6). In SFD infants the incidence of acidosis is also clearly higher than in AFD infants (Low et al. 1972 and 1978, Jurgens-vd Zee et al. 1979, Huisjes et al. 1980- table 6). The incidence of acidosis in SFD infants increases further with increasing severity of IUGR (Huisjes 1981). The association IUGR-Acidaemia can be explained by the higher susceptibility of the SFD fetus and the marginally functioning placenta during the stress of labour. SFD fetuses demonstrated a significantly higher lactate level in fetal scalp blood (an increased likelihood of metabolic acidosis) especially in the presence of fetal heart rate (FHR) decelerations compared to AFD fetuses (Lin et al. 1980). Mostly preterm and/or SFD infants were involved in cases where severe cerebral injury was associated with a more severe metabolic acidosis at delivery (Low et al. 1977). Huisjes et al. (1980) observed a high prevalence of neonatal neurological abnormalities in subjects who were both growth retarded and acidaemic. In the group with a birth weight centile $< 2.3$ (n=97) the proportion of neurologically abnormal infants was double that of the group with a birth weight centile $<$ 10th (n=361), i.e. 19.2% versus 8% (Huisjes 1981).

### 2.7.2. Relationship between umbilical cord acid-base values and the neurological condition in later life

Although many reports have recorded the association between asphyxia at birth and later neuro-developmental disability, the significance of asphyxia remains uncertain.

Discrepancies in the associations found in this context may, to a large extent, be due to the fact that perinatal hypoxic insults vary from mild to severe, the response of the individual fetus and neonate are influenced by concurrent risk factors such as prematurity and IUGR, and that variable definitions of significant

hypoxia can be used. Severe intra-partum hypoxia may result in hypoxic-ischaemic encephalopathy in the neonate (Brann & Dykes 1977). Approximately 30% of the surviving infants demonstrated late neurological sequelae in clinical studies of neonates with severe intra-partum hypoxia (Finer et al. 1981, Brown et al. 1974). One of the best means to determine hypoxic episodes experienced by the human fetus is an acid-base assessment of the fetal blood during labour and delivery. There are, however, no absolute values of $pO_2$, $pCO_2$ and pH at which irreversible brain damage can be said to occur in the newborn infant. The excellent long-term outcome in a case report of a child with a $pH_{ua}$ of 6.60 (Fysh et al. 1982) supports the belief that the detection of an extremely severe acidosis is not inevitably associated with ultimate brain damage. In a recent study of 60 infants with biochemical evidence of intra-partum fetal hypoxia (umbilical buffer base of less than 34.0 meq/l), Low et al.(1984) showed that the degree and duration of fetal hypoxia are the distinguishing features between children with motor and cognitive deficits and children without at one year of age. The incidence of deficits increased from 20% to 80% as the buffer base decreased from 30-34 meq/l to less than 22 meq/l. Additionally, the duration of the developing metabolic acidosis was in excess of one hour in children with deficits, whereas it was less than one hour in normal children. They also found motor and cognitive deficits in approximately 50% of the children when an episode of asphyxia of more than one hour resulted in a metabolic acidosis to the order of 25 meq/l. The severity and duration of fetal hypoxia in this context is very important as can be seen from the fact that the effect of fetal hypoxia, without encephalopathy in the neonate, seems to be far less dramatic. In a follow-up study of 37 AFD term infants, who had terminal episodes of intra-partum fetal hypoxia (lasting less than one hour) without encephalopathy, no neurological and/or mental handicaps were found at one and five years of age (Low et al. 1983). This author proposed that "the asphyxia experienced by these mature fetuses was not as severe as the critical level leading to CNS injury and residual disability in the surviving children." Also in AFD term infants Aarnoudse et al. (1985) recently demonstrated that severe fetal hypoxia, as indicated by an umbilical artery pH $\leq$ 7.00 (n=46), is not a major

cause of later neurological sequelae at two and a half to nine years of age. Major neurological abnormalities were not found and minor neurological dysfunctions were only found in four infants (7%).

It is evident that other characteristics (e.g. prematurity and growth retardation) of the stressed fetus must be taken into account besides the severity of asphyxia. As mentioned before, the prognosis of AFD term infants with profound metabolic acidosis at birth seems to be good nowadays if the patients are actively managed with modern resuscitation and neonatal care techniques. The low correlations found in clinical studies between metabolic acidosis and immediate and long-term neurological outcome in especially AFD term infants indicates that with the improved fetal monitoring of the last decade fetal hypoxia can be identified at an early stage, before fetal compromise has occurred. There is more consensus in literature about the possible deleterious effect of acidosis in very low birth weight (VLBW) or growth retarded infants. The combination of VLBW with "presumed severe hypoxia" was related to later handicap in a study by Stewart & Reynolds (1974). Cormey & Fitzharding (1979) also found a strong association between handicap rate and perinatal asphyxia experienced by premature SFD fetuses. Aarnoudse et al. (1985) showed that in a group of 32 preterm severely hypoxic infants ($pH_{ua} \leq 7.00$, 11 were SDF) six (18.7%) were severely handicapped in later life compared to two (6%) in a control group of preterm/SFD infants with a $pH_{ua} \geq 7.20$ (n=37). Also Westgren et al. (1984) found a much higher rate of neurological abnormalities in the neonatal period and neurodevelopmental disabilities at two year follow-up in preterm infants with intra-partum acidosis than in non-acidotic preterm infants. In 86 SFD fetuses, of whom 93% were mature at birth, the occurrence of an episode of intra-partum metabolic acidosis was not found to be accompanied by major neurological abnormalaties and/or low Bayley scores at 12 months of age (Low et al. 1978).

The results of the neurological follow-up examination of the total SFD and preterm infant study group at our hospital only showed a relationship between acidaemia at birth and neonatal neurological morbidity (Huisjes et al. 1980). This relationship could no longer be demonstrated at 1.5 (Bierman-van Eendenburg et

al. 1981), 4 (Touwen et al. 1982) and 6 years of age (Hadders-Algra et al. 1986).

## 2.8. Relationship between Apgar scores and fetal/umbilical blood gas and acid-base values

There is a relationship between fetal acidosis and the poor condition of a baby at birth, as judged by Apgar scores, but the precision of this relationship leaves much to be desired. Many authors (Beard et al. 1967, Wood et al. 1967, Hon et al. 1969, Bowe et al. 1970, Haesslein & Niswander 1980) report a significant number of neonates with a scalp pH of above 7.20 with low Apgar scores (false normal pH) and a significant number of babies with a pH of 7.20 or less with normal Apgar scores (false abnormal pH) (see table 7).

These findings indicate that the use of fetal scalp blood sampling as a confirmatory diagnostic technique of in utero fetal asphyxia, is less precise than is usually thought for accurately identifying infants who will have low one and five minute Apgar scores. While Hon thought that many of these discrepancies could be accounted for by a prolonged interval between sampling and delivery, the poor correlation in many cases could still be explained. In our study similar rates of false positive and false negative umbilical cord pH values were obtained (Table 7). A variety of factors were found to account for this lack of correlation. The most notable factor contributing to the rate of false abnormal values is maternal acidosis. Sedative drugs or aneasthetics, infections, congenital anomalities, prematurity and maternal alkalosis explain a low Apgar score with normal pH values (false normals) (Bowe et al. 1970).

In most studies highly significant relationships were found between fetal pH (scalp pH and umbilical cord pH) and Apgar scores, indicating that high pH values are associated with high Apgar scores and low pH values with low Apgar scores. Beard et al. (1967) showed a clear positive linear relationship between these measurements by calculating mean pH values for paired Apgar scores

Table 7. Prediction of Apgar scores from fetal scalp or umbilical artery pH values by several authors

| | 0 - 6 | 7 - 10 | |
|---|---|---|---|
| fetal scalp pH / umbilical artery pH | % false normal pH<br>Bowe (1970) - 10.4 (1min)<br>Beard (1967) - 9.0 (2min)<br>Wood (1967) - 38.0 (2min)<br>Haesslein (1980) - 22.0 (5min)<br>Hon (1969) - 17.5 (1min)<br>Hon (1969) - 4.3 (5min)<br>Tejani (1976) - 8.5 (1min)<br>Dijxhoorn (1986) - 2.3 (1min) | | |
| >7.20 | | | |
| ≤7.20 | | % false abnormal pH<br>Bowe (1970) - 7.6 (1min)<br>Beard (1967) - 14.0 (2min)<br>Wood (1967) - 4.2 (2min)<br>Haesslein (1980) - 7.3 (5min)<br>Hon (1969) - 10.0 (1min)<br>Hon (1969) - 26.0 (5min)<br>Tejani (1976) - 11.0 (1min)<br>Dijxhoorn (1986) - 32.3 (1min) | fetal scalp pH<br>umbilical artery pH |

Apgar score

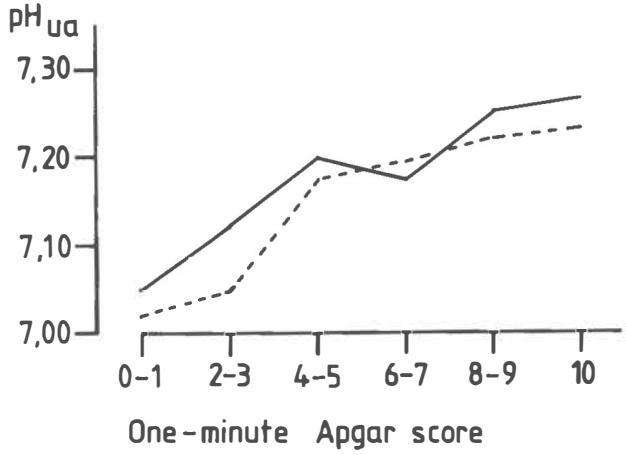


Figure 1. Mean actual pH values for paired two-minute Apgar scores (Beard 1967- solid line) and one-minute Apgar scores (Dijxhoorn 1986- broken line).

(figure 1). From this figure, in which our data are presented with a broken line, it can be seen that not only is the presence of a low pH important but also the severity of acidosis. Wood (1978) showed that when the fetal pH was $< 7.10$ about two in three of these babies had a very low Apgar score (0-3). Sykes et al. (1982), found however, that 73% (56/57) of the infants with severe acidosis at birth ($pH_{ua} \leq 7.10$) had an Apgar score $\geq 7$ at one minute and 86% had an Apgar score $\geq 7$ at five minutes. Only 21% (20/97) of the infants with a one minute Apgar score $\geq 7$ showed severe acidosis, indicating that it is possible for asphyxial damage to occur without depression at birth.

Despite the statistically highly significant correlation between fetal pH and Apgar score (Marx et al. 1977, Bowe et al. 1970: $p < 0.001$), fairly low correlation coefficients were found (Renou et al. 1976: $r=0.32$, Marx et al. 1977: $r=0.45$, Bowe et al. 1970: $r=0.48$). The correlation coefficients for fetal pH and Apgar scores of 7-10 are especially poor (Hon et al. 1969: $r=0.08$, Dyxhoorn 1986: $r=0.10$), whereas for Apgar scores of 1-6 the

correlation coefficients are a great deal higher (Hon et al 1969: r=0.60, Dyxhoorn et al. 1986: r=0.24).

Some authors have presented evidence that fetal pH correlates better with the one minute Apgar score than with the five minute Apgar score (Hon et al. 1969). Fetal $pCO_2$ (Khazin et al. 1969) and base defecit (Khazin et al. 1969, Beard et al. 1967) have also been correlated with Apgar scores, but the correlation coefficients were poor. Comparison of the fetal base defecit with the Apgar score showed no closer relationship than that obtained with the use of pH values. This is probably due to the fact that the fetal base defecit and pH values do not exclude the influence of maternal acidosis.

In an effort to decrease the rate of false normal and false abnormal pH values (Bowe et al. 1970, Beard et al. 1967), determination of ΔpH and Δ BE (differences between maternal and fetal pH and base excess values) were put forward as being additionally valuable parameters for assessing fetal condition. This was based on the idea that there is a reflection of increasing maternal acidosis or alkalosis during labour in the fetal compartment which is not necessarily deleterious to the fetus. Bowe found that ΔpH and ΔBE were 0.21 U and 4.8 meq/l respectively in acidotic mothers with acidotic fetuses. The fetuses were nevertheless vigorous at birth (Apgar score $\geq$ 7). In comparison, ΔpH and ΔBE values were 0.27 U and 7.0 meq/l when the infant was both acidotic and depressed at birth. Using the ΔpH and especially the ΔBE values, Bowe was able to diminish the rate of false abnormal values. Paying attention to maternal hydration and caloric requirements will decrease the proportion of infants in the false abnormal group. The proportion of infants in the false normal category will be influenced by both the practice of obstetrics and obstetrical anaesthesia. The rate of "false" categories may, therefore, vary from clinic to clinic. There is little data in literature on the correlation between ΔpH and ΔBE and the Apgar scores. Closer correlation coefficients are expected when all the values are considered together instead of just the pH or BE values alone.

Krause et al. (1978) could not confirm these expectations for ΔpH values, whereas the correlation coefficient for Δ pH and the one

minute apgar score was lower than for $pH_{ua}$ and the same Apgar score ($r=0.32$ and $r=0.51$ respectively) (note Dyxhoorn 1986: $r=0.16$ and $r=0.21$ respectively).

## 2.9. Combination of Apgar scores and umbilical acid-base status in relation to neurological outcome

Is the prognosis of brain development poorer if both acidosis and low Apgar scores are present at birth? Sykes et al. (1982) mentioned that it would seem logical to look more closely at the infants who had both low Apgar scores and low pH values at birth (2.2% in his study). Information about the relationship between the combination of these two indicators of asphyxia with the neurological outcome is not yet available in literature.

Only Litschgi et al. (1974) found proportionally the lowest one and five minute Apgar scores as well as the most neonatal neurologically non-optimal infants in his study on infants born with severe acidosis ($pH_{ua} \leq 7.09$). However, in one third of these cases prematurity might have biased the results. Whether the umbilical cord blood results are of greater predictive value, concerning neurological outcome, than the Apgar scores, or vice versa, is still an open question.

For Goldenberg et al. (1984) it remained unclear whether it was the Apgar score or the umbilical artery pH value which was the best predictor of neonatal mortality or long-term neurological sequelae in the preterm infant. These authors observed a change in the relationship between the Apgar score and pH value as the gestational age advanced. The more premature the infant, the more likely it is to find a low Apgar score in the presence of a $pH \geq 7.25$. Conversely, an Apgar score of $\geq 7$ in the presence of a pH of $< 7.25$ becomes more frequent closer to term. The authors suggested that the predictive value of one or both measurements may vary with the gestational age. They could not confirm this suggestion due to the absence of a classification for neorological outcome in their study.

## 2.10. Meconium stained amniotic fluid

Meconium stained amniotic fluid (MSAL) during labour in cephalic presentation is said to be a potentially ominous indication of fetal condition. However, controversy exists regarding the relative importance of this sign compared to other factors which indicate fetal distress.

Several mechanisms have been suggested relating hypoxaemia to the passage of meconium in utero. Reed (1918) and Brews (1948) suggested that anoxia causes the anal sphincter to relax and meconium subsequently passes into the surrounding amniotic fluid. Saling (1962) postulated that fetal hypoxia precipates vasoconstriction in the fetal gut which causes hyperperistalsis, sphincter relaxation and the passage of meconium. Further data on meconium passage were gained in 1954 when Walker found that fetuses at term with MSAL had a lower umbilical vein oxygen saturation than fetuses without MSAL.

The average incidence of MSAL in literature is 11% (8-15%). Comparing results in literature, the TYPE (thick or thin: heavy or light) and TIME of passage (early or late in labour) are the most significant factors affecting fetal outcome. Meis et al. (1978) therefore presented a classification for MSAL: (A) Early light group 54% (in which no association was found with an increased intra-partum or neonatal morbidity or death), (B) Early heavy group 25% (in which increased intrapartum or neonatal morbidity, death and antecedent obstetric problems were found), (C) Late passage 21% (which was not associated with perinatal losses, but with an increased neonatal morbidity occurring late in labour, for instance meconium aspiration syndrome).

### 2.10.1. Meconium in relation to Apgar score and/or fetal/umbilical acid-base

Heavy, thick meconium noted early in labour, for instance at the time of rupture of the fetal membranes, suggests fetal asphyxia. It correlates strongly with fetal hypoxia/acidosis in early labour, in contrast to thin and absent meconium, and is predictive of low one and five minute Apgar scores.

In the overall comparison of meconium and non-meconium

patients the mean one and five minute Apgar scores were found to be lower in the meconium group (Starks 1980 and Miller et al. 1975). Regarding the meconium subgroups, the majority of patients with a low one minute Apgar score (<7) fall into the thick meconium group (64%), compared to 4.5% in the thin meconium group and 8% in the control group.

Hobel (1971) and Starks (1980) found significantly lower scalp pH values in early labour (cervical dilation 3cm or less) especially in the heavy meconium group, as compared to the non-meconium group. This suggests that the insult responsible for the acidosis had occurred before or at the onset of labour. Low et al. (1981) found the presence of meconium to be associated with an increased probability of metabolic acidosis for all fetal weights and for all gestational ages. This association, between meconium and acidosis, was not found by Miller et al. (1975). Even in his thick meconium group the fetal scalp pH was not significantly different from that in the non-meconium group. His data indicated that without signs of fetal distress ("late" fetal heart rate (FHR) decelerations) meconium does not predispose to poor outcome.

All these observations confirm that especially thick meconium should serve to alert the physician to a possible high-risk fetal condition. All patients with MSAL should be primarily managed in labour with continuous FHR monitoring. If any "abnormal" FHR changes are noted, fetal blood sampling for acid-base state is indicated for additional management. Special care must be taken to avoid conditions which would cause fetal asphyxia, such as those caused by uterine hyperstimulation and maternal hypotension etc. Every attempt should be made to avoid difficult and/or traumatic delivery with the inherent increase in fetal compromise and asphyxia. At delivery the trachea and pharynx should be aspirated carefully in an attempt to avoid aspiration. The overall incidence of the meconium aspiration syndrome in live-born infants is 1 to 3%. Between 10 and 30% of MSAL babies develop varying degrees of respiratory difficulties (Gregory et al. 1974). In the past meconium aspiration has been regarded as an entirely neonatal event. More recently, however, meconiun aspiration in utero has been suggested in more and more cases (Brown & Gleicher 1981). Hypoxia may not only cause the passage of meconium but it may also

result in periodic spontaneous respiration, i.e. the aspiration of meconium prior to delivery. Fetuses who pass late heavy meconium have the greatest morbidity rate as a result of meconium aspiration.

### 2.10.2. Meconium in relation to the neurological condition

It seems reasonable to relate meconium with possible neurological sequelae especially due to the significance of meconium as a possible sign of fetal distress/hypoxia. There is little known about this subject in literature. Nelson & Broman (1977) found the presence of meconium, as an index of asphyxia, more frequently in the severely handicapped group than in the control group (41%,n=20 vs. 19%,n=9; $p<0.001$).

In the following chapters evidence will be provided which indicates that the presence of meconium is not related with the neonatal neurological condition.

## 2.11. Discussion

Reviewing the literature, it is not easy to compare the results of various studies regarding the consequences of asphyxia at birth in relation to neonatal and/or brain functioning in later life. This is mainly due to the lack of uniformity in obstetric management and dissimilarities in the obstetric study groups. The definition of birth asphyxia is very vague and therefore, a wide variety of often inaccurate or imprecise definitions have been used. Studies on infants born after severe birth asphyxia showed that the prognosis for surviving infants is better than had been thought. Despite these data a tendency exists to overestimate the risk of handicap caused by asphyxia at birth.

In general the literature shows that preterm birth, intra-uterine growth retardation and the presence of hypoxic-ischaemic insults are major factors affecting the prognosis. In order to interpret these data correctly it is necessary to take important factors into account, viz. the definitions of prematurity, IUGR and asphyxia.

The definition of prematurity, for instance, is often based on the birth weight instead of on the duration of pregnancy. Low birth weight is very often thought to be concomitent with premature birth. Therefore, universal definitions must be used in order to create uniformity in the classification of neurological development.

Hypoxic-ischaemic insults caused by perinatal asphyxia may lead to brain injury and give rise to specific neurological abnormalities in the newborn period or result in residual motor and cognitive defects in children who survive.

Distinct neuropathological varieties have been demonstrated in human neuropathological examinations of the brain. Even so, the aetiology of cellular damage of the CNS in asphyctic fetuses remains controversial. As can be seen from figure 2, it is probably not hypoxaemia alone, but a multitude of events that explain the distribution of cellular damage in the brain.

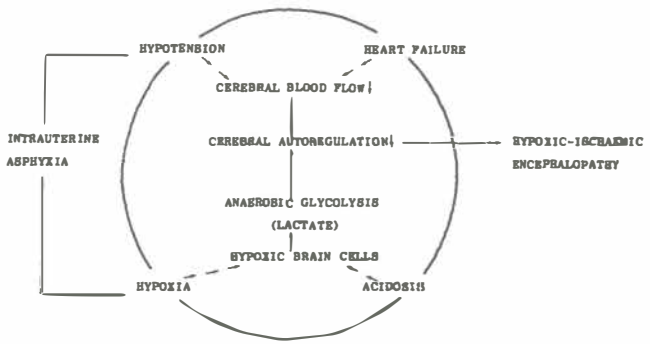


Figure 2. Asphyxia and sequences in fetal cerebral metabolism.

Also, decreased oxygen content of the brain tissue cannot be

measured directly so one has to rely on biochemical indications of hypoxia, e.g. acidaemia. Whether fetal and/or umbilical acid-base values reliably predict damage to the nervous system remains to be seen. The introduction of ΔpH and ΔBE as additional acid-base parameters perhaps makes it possible to assess the true state of a fetal pH/BE decrease more accurately. Data concerning the relationships between these parameters and neurological sequelae are not yet available in the literature.

The Apgar scoring system is one of the most frequently used indices of birth asphyxia, but its validity has recently been questioned.

Meconium stained amniotic fluid, as a sign of fetal distress, was only found to be related with neurological sequelae in one study.

Despite the fact that numerous definitions have been used for birth asphyxia it is quite evident that the degree to which it contributes to neurological and developmental abnormalities depends on the duration and severity of the asphyxial events.

It has become clear from reviewing the literature that the identification of perinatal problems and newborn management have greatly improved over the last two decades. Data obtained from 1950 to 1970 may be unduly pessimistic nowadays.

Most morbidity investigations diverge in their methodology and are often liable to criticism.

Before describing patients and methods I will try to outline some criticisms about the methodology of morbidity examinations used in the literature.

- Most studies were performed in retrospect and involved selected populations. It is a well-known fact that problems arise in composing a control group in retrospective studies. Numerous, quite different definitions have been used to define morbidity. One often has to rely on the memory of the people questioned, which increases the unreliability of the results.
- Many follow-up studies lacked a control group and contained a large number of patients who dropped out.
- Many study groups were limited in number or consisted of only a small percentage of the original population, therefore making it impossible to generalise the results.

- Duration of pregnancy and birth weight were often not regarded as separate variables in the analysis.
- Follow-up examinations were carried out on children of different ages. One should take into account the specific qualities of the central nervous system with relation to age.
- Scarcely standardized age-specific testing methods were applied, which may result in low test-retest and low inter-observer reliability.
- Especially in retrospective studies, attention is seldom paid to possible interval complications.
- Results from long-term follow-up are often already out of date because obstetric techniques and neonatal care have been changed. In most studies, however, this is unavoidable.

In chapter 3, where the present study group and methods of investigation are described, we have tried to find solutions for these problems as much as possible.

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*Chapter 3*

# SUBJECTS AND METHODS

## 3.1. Selection of subjects

The children studied were born between June 1975 and July 1978 at the Obstetrical Department of the University Hospital in Groningen. This hospital is a regional centre for advanced perinatal care. The patient population visiting the Department of Obstetrics can be considered as a negative selection because of the traditionally high (40%) proportion of home deliveries and the overrepresentation of patients with serious obstetrical problems or a poor obstetric history. From the point of view of the study the wide range of subjects from normal to highly pathological was considered advantageous. The fact that we studied a non-representative sample of the population was not thought to be a disadvantage: handicap rates may vary with the population studied, but the relationship between sequelae and perinatal events should not.

The infants studied in this thesis are all part of the so-called "Groningen Perinatal Project" (GPP), which is a prospective longitudinal survey with the aim of detecting relationships between pre- and perinatal circumstances and the development of the nervous system. The GPP consists of two consecutive 1.5 year cohorts of 1581 and 1729 infants respectively (Jurgens-van der Zee et al. 1979 and Huisjes et al. 1980). Of these 3310 infants, 80 died perinatally (Table 1), which amounts to a perinatal mortality rate of 24 per thousand. Another 62 infants (2%) could not be examined for various reasons (early discharge of transfer to another hospital n=48, work overload n=9, or parents declined the examination n=5). This attrition rate of 2% is low, so that this methodological problem was not thought to be of any great significance. As a result, a total of 3162 singleton infants (1507 and 1655 in the two birth cohorts) could be submitted to a neonatal

neurological examination and a pediatric screening. The groups studied and discussed in the following chapters all form part of this total cohort of 3162 infants.

Table 1. Causes of perinatal deaths

| | First cohort | | Second cohort | |
|---|---|---|---|---|
| | Intrauterine | Neonatal | Intrauterine | Neonatal |
| IUGR * | 6 | - | 8 | 1 |
| Preterm birth | - | 5 | - | 9 |
| Abruptio plac. | 3 | - | 2 | - |
| Congenital Abn. | 2 | 7 | 3 | 8 |
| Other causes | 9 | 5 | 10 | 2 |
| Total | 37 | | 43 | |

* IUGR= intra-uterine growth retardation
(Huisjes et al. 1980), (with permission)

After surveying the literature it was concluded in Chapter 2 that in a study of the relationships between asphyxia at birth and the neonatal neurological condition it is important to distinguish between infants born appropriate-for-dates (AFD) and small-for-dates (SFD) and also between those born at term and preterm. In order to examine the role of labour and delivery in causing or worsening "asphyxia" in a population, it is desirable to make a distinction between deliveries by the viganal route or by Caesarean section (CS). Additional reasons for separate consideration of infants born by CS are the effects of maternal ventilation on fetal blood gas values during CS and the preselection of already compromised fetuses by, for example chronic placental insufficiency, signs of intra-uterine asphyxia, severe growth retardation, etc.

In the following chapters the relationship between indices of asphyxia at birth and the neonatal neurological condition will be studied in the following subgroups:

- Chapter 4 and 5- AFD infants (birth weight above 10th centile) born vaginally at term (gestational age more than 37 completed weeks) (n=805) with a complete record of the maternal and umbilical artery blood gas acid-base status (including pH, $pO_2$, pCO and base excesses).

- Chapter 6- SFD infants (birth weight below the 10th centile, born vaginally (n=224) or by CS (n=23), at term with a known umbilical artery pH.
- Chapter 7- AFD preterm infants (gestational age less than 37 completed weeks) (n=93) and SFD preterm infants (n=33) with a known umbilical artery pH.

The composition of the study populations will be discussed further in the appropriate chapters.

## 3.2. Collection of perinatal data

In all cases extensive obstetrical and immediate neonatal data were collected, documented on precoded proformas and stored in a computer file. From the data, 74 variables were selected which were considered representative of pregnancy, delivery and condition of the infant immediatly after birth (Touwen et al. 1980). The 74 variables were grouped according to seven aspects: social background, non-obstetrical conditions during pregnancy, obstetrical past history, obstetrical aspects of pregnancy, diagnostic and therapeutic measures, labour and delivery and neonatal condition immediately after birth. Particulars concerning some of these aspects in both cohorts were given by Jurgens-van der Zee et al. (1979) and Huisjes et al. (1980) and will therefore not be discussed in this thesis. A remarkable observation was the low rate of preterm infants (171/3162=5.4%) which is probably mainly due to the fact that stillborns and neonatal deaths were excluded from this study.

The collection and classification of neonatal neurological data will be discussed under 3.3.2.

## 3.3. The neonatal neurological assessment

### 3.3.1. Why an examination in the neonatal period?

Impairment of brain function, even if transient and without dramatic permanent handicaps, should be a matter of concern to the obstetrician. Especially the short-term effects of his or her

management are important in order to judge its efficiency. Long-term morbidity of the brain is of limited value for this purpose because between birth and follow-up numerous factors, such as intercurrent disease or mechanisms of compensation during development, can obscure relationships between obstetrical data and neurological findings in later life (Touwen et al. 1982). In the Groningen Perinatal Project no specific obstetrical conditions were found to be related with late neurological sequelae at four and six years of age (Touwen et al. 1982 and Hadders-Algra et al. 1986).

Neonatal neurological examination has been shown to be an important instrument in the evaluation of the short-term morbidity of the neonate's brain (Jurgens-van der Zee et al. 1979, Huisjes et al. 1980). Adverse influences during labour and delivery are known to be related to neonatal neurological dysfunction (Prechtl 1968, Touwen et al. 1980) and neonatal neurological findings can be used to select infants who should be followed-up during the first years of life. Yet, studies which use the neonatal neurological examination as a parameter of neonatal morbidity are scarce. The reasons for this scarcity are not clear. The inadequacy of assessment methods derived from adult neurology are probably (partly) responsible. The infantile brain is indeed different, qualitatively and quantitively from the brain of older children or adults, therefore specific and strictly age-appropriate, and standardized techniques are required. In the GPP such an examination method was applied (designed by Prechtl 1977).

### 3.3.2. Collection of neonatal neurological data

The neurological data were semiquantitatively recorded on precoded proformas and stored in a computer file. The neurological conclusion was recorded quantitatively by means of the so-called neurological optimality score and qualitatively as a neurological diagnosis.

#### 3.3.2.1. The optimality concept: Obstetrical and neurological optimality score

In large prospective studies (Graham et al. 1962, Niswander et

al. 1966) it was shown that a combination of prenatal and neonatal events might be more predictive of neurological outcome than single obstetrical events. Niswander observed that abruptio placentae or prolapse of the umbilical cord caused an increase in perinatal mortality, but the neurological examination results in this group at one and four years of age were comparable to those in the control group. However, the combination of these obstetrical complications with low Apgar scores and an abnormal neonatal neurological condition gave a much better prediction of deviant neurological preformance at one year of age. Such combinations still require a definition of abnormality and clear cut criteria for complications. In order to avoid this difficulty and that of attributing weights to particular complications, Prechtl (1968 and 1980) introduced his "optimality concept". The rationale of this concept is that an optimal range or value of an obstetrical (or neurological) variable can be defined more easily and accurately than a normal range or value. Implicit in this reasoning is that "optimal" is always normal, whereas normal is not necessarily optimal. If a particular value of a variable deviates away from the optimal range (i.e. "abnormal" in a clinical sense), this variable will rarely occur alone. It is usually accompanied by other non-optimal variables. Therefore, the system is self-weighting and the weighting of specific isolated variables is not necessary.

An optimal range was defined for a representative and comprehensive list of pre- and perinatal variables to describe the condition of the mother, the fetus and the placenta, consisting of those values which carried the least possible risk for the infant's health. Originally a list of 42 obstetrical conditions was created (Prechtl et al. 1968); later the list was extended to 74 items (Touwen et al. 1980). As already mentioned in 3.2 (page 62), the variables on the latter list were categorized to describe seven aspects of pregnancy and delivery. By giving a point for each item meeting the defined optimality criterion, the number of items outside the optimal range gives a score of reduced optimality.

In the GPP the optimality concept was also applied to the neonatal neurological findings, using a representative list of 60 items and resulting in a neonatal neurological optimality score (NNOS) (Touwen et al. 1980). This quantified scoring of the

neonatal neurological examination results complements the clinical neurological diagnosis.

3.3.2.2. The neonatal neurological diagnosis

The clinical diagnosis was made according to the descriptive neonatal neurological syndromes listed in Table 2 (Jurgens-van de Zee et al. 1979). For practical reasons the diagnoses were

Table 2. Classification of possible neonatal neurological syndromes

| | |
|---|---|
| 1. Increased or decreased excitability | Hyperexcitability syndrome<br>Convulsions<br>Apathy syndrome<br>Coma |
| 2. Increased or decreased motility | Hyperkinesia<br>Hypokinesia |
| 3. Increased or decreased tonus | Hypertonia<br>Hypotonia |
| 4. Asymmetries | Peripheral- e.g. lesion of a plexus<br>Central - e.g. hemisyndrome |
| 5. Defects of the CNS | Spina bifida |
| 6. Combinations | |

Abnormal = presence of one or more of these syndromes
Suspect = some symptoms of one or more of the syndromes
Normal = none of the syndromes
(Jurgens-van der Zee et al. 1979, with permission)

classified qualitatively using the categorizations "normal", "suspect" or "abnormal". An infant was considered to be neurologically abnormal if one of the syndromes on the list was present. An infant was classified as suspect if only isolated symptoms or complete syndromes of very low intensity were found, e.g. an isolated tremor or a mild hypotonia. Table 3 presents the distribution of the neurological syndromes in the total group of 3162 infants (Huisjes et al. 1980).

Table 3. The distribution of neurological syndromes in both cohorts

| | 1st Cohort | 2nd Cohort | Total |
|---|---|---|---|
| Hyperexcitability syndr. | 10 | 13 | 23 |
| Apathy syndr. | 2 | 7 | 9 |
| Severe hypotonia | 28 | 14 | 42 |
| Severe hypertonia | 4 | 5 | 9 |
| Asymmetries - central | 10 | 3 | 13 |
| - peripheral | 11 | 14 | 25 |
| - unknown origin | 1 | 2 | 3 |
| Combinations | 14 | 23 | 37 |
| Total | 80 | 81 | 161 |

Combinations consisted of one syndrome accompanied by another syndrome or a few signs belonging to other syndromes (Huisjes et al. 1980 with permission)

As mentioned above, the quantitative and qualitative appraisals are complementary. Within the diagnostic subgroups "normal", "suspect" or "abnormal", the neurological optimality scores make it possible to quantify the neurological condition, thereby grading the severity of the neurological condition.

### 3.3.3. The standardization of the neonatal neurological examination

The neonatal neurological examination was carried out according to the technique described by Prechtl (1977). The examination was performed between the 4th and 8th day of life because from that age onwards neurological findings have been shown to be more consistent than those shortly after birth (Beintema 1968). The infant takes at least three days to adapt to the extrauterine situation. The biochemical and physiological values vary considerably in this period and this lack of homeostasis influences the neurological results.

Infants born prematurely were examined at term gestational age, as standardized neonatal examination techniques are obviously not available for preterms. Moreover, in the absence of serious neonatal complications the rate of intra- and extra-uterine maturation of the CNS is comparable (Touwen 1980), therefore term age standard data can be applied to infants originally born prematurely. The neurological examination procedures were

standardized in order to ensure a good test-retest and inter-observer reliability. Special attention was paid to conditions such as environmental temperature (27-30 °C), light intensity, the post-prandial time and technique of handling the baby. Obviously, conditions that could affect the results of the neurological examination (e.g. jaundice, dehydration, hyperthermia etc.) were recorded.

Besides the comprehensive neonatal neurological examination, a short pediatric screening was carried out by the consultant pediatrician consisting of a general examination and an assessment of the gestational age according to Farr et al. (1966).

### 3.4. Discussion

In the literature many of the investigations into the consequences of asphyxia at birth were based on neurological findings in later life and were performed retrospectively (see Chapter 2). However, long-term results of neonatal problems, such as asphyxia, are confused by possible intercurrent complications and/or recovery processes.

The follow-up studies of the GPP show that the majority of neonatally neurologically deviant infants recover. The studies also show that in the absence of intervening complications, later abnormal infants are mainly found in the neonatally abnormal groups (Bierman-van Eendenberg et al. 1980), Touwen et al. 1982, Hadders-Algra et al. 1986). However it is virtually impossible to perdict which infant will recover and which will develop a neurological abnormality (Touwen et al. 1982). Therefore, if one wishes to estimate the contribution of asphyxia at birth to the aetiology of neurological impairment, the evaluation of the neonatal neurological condition appears to be the best strategy. For this reason the design of the investigation in this thesis is based on analysing the relationship between neonatal neurological morbidity and asphyxia at birth. Another reason for not taking later neurology into account in this thesis is the fact that any relationship which was found in the GPP between neonatal neurology and variables of asphyxia at birth (Huisjes et al. 1980) had disappeared in later life (Touwen et al. 1982). Only some brief

remarks on later outcome in SFD at term and in preterm infants will be given in Chapter 6 and 7 respectively.

In Chapter 3 some remarks on the investigation techniques applied and the collection and classification of data concerning obstetrics and neonatal neurology are given. No attempt was made in this section to describe the statistical methods used, as they will all be mentioned in the following chapters.

The selection of the study groups was made according to the presence or absence of preterm birth and/or growth retardation, because neonatal neurological morbidity may be a cumulative effect of these attendant circumstances, rather than the exclusive effect of birth asphyxia. It is also important to make these selections due to the fact that the majority of follow-up studies in the literature only include low birth weight infants, without making a differentiation according to birth weight in relation to gestational age. The importance of differentiating between AFD and SFD infants and between term and preterm infants, when asphyxia at birth is involved, will be dealt with in the following chapters.

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*Chapter 4*

# The relation between umbilical pH values and neonatal neurological morbidity in full term appropriate-for-dates infants

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Accepted for publication 29 November 1984

**Summary**

The relationship of umbilical cord pH with the neonatal neurological condition was investigated in a group of 805 appropriate-for-dates (AFD) infants, delivered vaginally at term, and in a subgroup of 205 infants born after uncomplicated pregnancy and delivery ('low-risk' group). The results of the neonatal neurological examination were expressed in a neonatal neurological optimality score (NNOS) and in a neurological classification (normal, suspect and abnormal). In both study groups a significant relation between umbilical arterial pH ($pH_{ua}$) and the difference between maternal venous pH and $pH_{ua}$ ($\Delta pH_{m\text{-}ua}$) on the one hand and neurologically suspect infants and NNOS on the other hand, was found. The percentages of explained variance in NNOS, however, were very low (for $\Delta$pH, 1 and 4% in the total and low-risk group respectively). Neurological abnormality was not related to acidaemia at birth. Because of the specific relation between maternal and umbilical pH, $\Delta$pH is a less reliable indicator of fetal condition in cases of maternal alkalosis or acidosis. The use of a $\Delta$pH corrected with the help of a maternal–fetal pH nomogram, however, only slightly improved the relation with neurological morbidity. It is concluded, that in AFD term infants acidaemia at birth is only slightly related to neonatal neurological morbidity.

appropriate-for-dates infants; neonatal neurological examination; acidaemia; perinatal complications; optimality score

*Early Human Development*, 11 (1985) 33–42
Elsevier

## Introduction

Brain damage can be the consequence of fetal hypoxic insults but the extent to which various degrees of hypoxia affect the nervous system is still under dispute [10,12]. This is probably due to dissimilarities in the obstetric populations studied, especially with regard to definition of such variables as obstetrical complications, gestational age and weight-for-dates of the infants, neonatal care and resuscitation facilities and strategy and technique of neurological examination and categorization.

In the human fetus the oxygen supply to tissue cannot be measured directly and therefore we have to rely on phenomena which are more or less related to hypoxia, such as measurements of biochemical consequences of hypoxia, e.g. acidaemia and decrease of buffer base. Clearly, there is a strong correlation between acid-base measures and fetal hypoxia [10], and some investigators consider umbilical pH as a reliable predictor of damage to the nervous system [9,18].

In the present investigation the relationship between umbilical pH and the neonatal neurological condition was studied in vaginally born appropriate-for-dates (AFD) term infants, with and without obstetrical complications. As both umbilical arterial pH and venous pH are influenced by maternal pH at delivery [2,16] the latter was also included in this study.

## Patients and Methods

In 1975 the Groningen Perinatal Project was started with the aim of studying the relationship between pre- and perinatal events and the development of the nervous system. Over 3000 singleton infants, consecutively born in the course of three years, underwent a standardized neonatal neurological examination [14]. Term infants were examined on the fourth or fifth postnatal day. The neonatal neurological condition was classified using a qualitative and quantitative approach. The qualitative approach entailed assigning each infant to one of three diagnostic categories: normal, suspect, abnormal. An infant was considered abnormal if one or more of the following neurological symptoms were present; hyper- or hypokinesia, hyper- or hypotonia, hemisyndrome, apathy syndrome, hyperexcitability syndrome. An infant was classified as suspect if only isolated symptoms were present, but no defined syndromes. A detailed description of this classification has been published elsewhere [7]. Another way used for quantifying the neurological findings was the optimality concept as described by Prechtl [15]. This entailed defining an optimal range for 60 representative neurological items. Each infant obtained a neonatal neurological optimality score (NNOS), consisting of its number of items falling within the optimal range (for details see Ref. 19).

The total study population consisted of 3162 singleton infants born between June 30, 1975 and July 1, 1978 in the Groningen University Hospital. For the present study those 986 cases were selected for whom complete neonatal (umbilical vein and artery) and maternal blood gas analyses were available. These cases were representative for the total group with respect to criteria such as maternal age, parity, neonatal

TABLE I

Selection criteria for the 'low risk' group ($n = 205$)

- Antenatal Obstetric Optimality score of 45 or higher
- No admission to hospital during pregnancy
- No meconium stained liquor amnii
- No drugs given during labour
- Duration of second stage of labour < 60 min
- Spontaneous vaginal delivery in vertex position
- No congenital malformations

neurological condition, Apgar score and the frequency of instrumental deliveries and breech deliveries. Thus failure to obtain all blood gas variables (including $pO_2$, $pCO_2$ and base excess), did not introduce any obvious selection bias. To exclude some other important factors influencing the neonatal neurological condition, preterm (< 37 completed wks) and growth retarded infants (< 10 birth weight percentile) [8] were excluded. In addition, Caesarean sections were excluded because of possible artificial effects of maternal ventilation on fetal blood gas values. The final study group consisted of 805 vaginally born appropriate-for-dates (AFD) term infants.

Because variables other than acidaemia which are associated with the neonatal condition are still present in this group, the significance of acidaemia at birth per se may be obscured or augmented. We therefore also selected a subgroup consisting of infants born after a 'low-risk' pregnancy and labour using criteria given in Table I.

The Antenatal Obstetrical Optimality Score (AOOS), as mentioned in this table, is part of the Total Obstetrical Optimality Score; this score consists of 74 items, relating to the antenatal, intra partum and immediate postnatal condition [19]. The antenatal part consists of 55 items; suboptimality was arbitrarily defined as a score $\leq 44$. Using all criteria mentioned in Table I, 75% of the infants had to be excluded, leaving 205 infants in the 'low-risk' group.

Blood from the umbilical vein and artery was collected anaerobically into heparinized polyethylene syringes, usually within 2 min after birth. The blood gas analysis was carried out immediately after the sample was obtained, or, if delay was necessary, after keeping it on ice. When preserved in this way, the pH will decrease at a rate of 0.007 U/h [20]. The maternal blood sample, from the cubital vein, was obtained within 10 min after birth and was analysed simultaneously with the umbilical cord blood samples in an I.L. 313 Digital pH blood gas analyser.

In addition to the more commonly used statistics, the relation between acidaemia and neonatal neurology was expressed as explained variance (multiple regression analysis). The predictive value of the independent variable increases with the percentage of explained variance of the effect-variable.

## Results

The neurological findings in the total study population and the low risk group are shown in Table II and Fig. 1. Although the morbidity was lower in the low risk

TABLE II

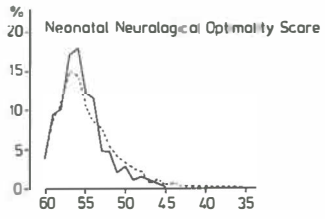
Distribution of neonatal neurological morbidity, expressed as a diagnostic category, in the total group ($n$ = 805) and in the low risk group ($n$ = 205)

| | Neonatal Neurological Diagnostic Category | | |
|---|---|---|---|
| | Normal | Suspect | Abnormal |
| Total group ($n$ = 805) | | | |
| $n$ | 619 | 156 | 30 |
| % | 76.9 | 19.4 | 3.7 |
| Low risk group ($n$ = 205) | | | |
| $n$ | 169 | 33 | 3 |
| % | 82.4 | 16.1 | 1.5 |

group, several infants in this group has a low neurological score and three were neurologically abnormal.

*(1) Total group (n = 805)*

The distribution of the umbilical artery pH ($pH_{ua}$) values in normal, suspect and abnormal infants is shown in Fig. 2. Suspect infants showed a statistically significant, but small shift to the acidaemic range as compared with normal infants (analysis of variance: $F(2,802) = 4.56$; $P < 0.025$). There was no difference in the distribution of pH values between neurologically normal and abnormal infants. Similar relations held for umbilical venous pH ($pH_{uv}$; not shown). Using the Neurological Optimality Score (NNOS), only with $pH_{ua}$ a significant relation was found (regression analysis: $F(1,803) = 3.02$; $P < 0.05$); with $pH_{uv}$ no such relation



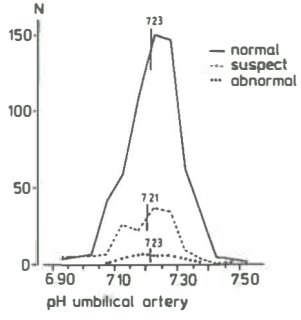




Fig. 1. Distribution of the neonatal neurological optimality score in the total ($n$ = 805, broken line) and low risk group ($n$ = 205, solid line).

Fig. 2. Distribution and median values of umbilical arterial pH in the three neonatal neurological diagnostic subgroups.

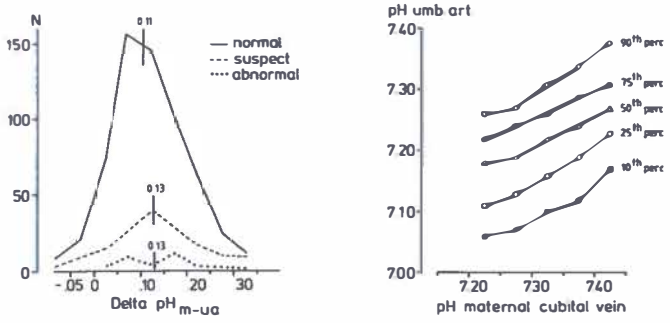



Fig. 3. Distribution and median values of maternal vein pH and umbilical arterial pH differences ($\Delta pH_{m\text{-}ua}$) in the three neonatal neurological diagnostic subgroups.

Fig. 4. Relation between maternal venous pH and umbilical arterial pH ($r = 0.39$), and maternal–fetal pH nomogram created after calculation of $pH_{ua}$ percentiles for varying maternal pH values.

could be demonstrated. The maternal cubital vein pH was not related to the neonatal neurological condition.

The relation between the neonatal neurological diagnosis and the difference between maternal venous pH and $pH_{ua}$ ($\Delta pH_{m\text{-}ua}$) is shown in Fig. 3. Both $\Delta pH_{m\text{-}ua}$ and $\Delta pH_{m\text{-}uv}$ were significantly higher in suspect than in normal infants ($F(2,802) = 3.96$ and 3.97, respectively; $P < 0.025$). The $\Delta pH$ differences between normal and abnormal infants were not significant, but the number of abnormal infants was very small. For the NNOS only a relationship with $\Delta pH_{m\text{-}ua}$ was found ($F(1,802) = 6.34$; $P < 0.025$). Although $\Delta pH_{m\text{-}ua}$ explained more of the variance in NNOS (0.8%) than did $pH_{ua}$ alone (0.4%), the percentage of explained variance was very low for both variables.

Using $pH_{ua}$ as an index of birth asphyxia, it is assumed that umbilical pH values are not influenced by maternal pH. On the other hand, using $\Delta pH_{m\text{-}ua}$ a constant difference between maternal and fetal pH at varying maternal pH values is suggested. However, neither of the assumptions is true: with increasing maternal pH the transplacental pH gradient gradually increases (Fig. 4). For instance, with a maternal pH of 7.20 $\Delta pH_{m\text{-}ua}$ is only 0.05 units, compared to 0.20 units with a maternal pH of 7.50. This increase can only in part be explained by the way pH is calculated from the actual hydrogen-ion concentration ($pH = \log(1/[H^+])$) and in the given example the transplacental hydrogen-ion gradient increases from 6 to 18 nmol/l. The most accurate way to assess the relation of NNOS with umbilical and maternal pH, therefore, is to use a regression analysis with $pH_{ua}$ and $pH_m$ as independent variables. Clinically this can be transformed into a maternal–fetal nomogram, with $pH_{ua}$ percentiles calculated for each maternal pH value (Fig. 4). Infants with a pH below the 10th percentile have to be considered the most acidaemic ones. With this corrected approach the variance explained in NNOS, however, did not evidently

TABLE III

Distribution of non-corrected and corrected $\Delta pH_{m\text{-}ua}$ values (percentiles) in the three neonatal neurological diagnostic subgroups

| $\Delta pH_{m\text{-}ua}$ (percentiles) | *n* | Neonatal Neurological Diagnostic Category | | |
|---|---|---|---|---|
| | | Normal (%) | Suspect (%) | Abnormal (%) |
| Not corrected | | | | |
| < 25 | 192 | 72 | 24 | 4 |
| 25–75 | 398 | 77 | 18 | 5 |
| > 75 | 215 | 81 | 17 | 2 |
| Corrected | | | | |
| < 25 | 192 | 71 | 25 | 4 |
| 25–75 | 398 | 77 | 19 | 4 |
| > 75 | 215 | 82 | 15 | 3 |

increase and the prediction of suspect infants was not improved as compared to the non-corrected $\Delta pH_{m\text{-}ua}$ (Table III).

*(2) Low risk group (n = 205)*

Elimination of additional variables with a possible effect on the neonatal neurological condition slightly improved the correlation between acidaemia and neonatal neurological morbidity. Significant relations were found between $pH_{ua}$ or $\Delta pH_{m\text{-}ua}$ and NNOS ($F(1,203) = 5.55$; $P < 0.025$ and $F(1,203) = 7.15$; $P < 0.01$, respectively), but the percentages of variance explained by pH values, although higher than in the total group remained low, 3.5 and 2.7%, respectively, for $\Delta pH_{m\text{-}ua}$ and $pH_{ua}$. The incidence of neurologically suspect infants was related to $pH_{ua}$ ($F(1,200) = 3.73$; $P = 0.05$) and $\Delta pH_{m\text{-}ua}$ ($F(1,200) = 4.59$; $P < 0.05$), but not to $pH_{uv}$ and $\Delta pH_{m\text{-}uv}$. The three infants diagnosed as abnormal had normal $pH_{ua}$ ($\geq 7.24$) and $\Delta pH_{m\text{-}ua}$ ($\leq 0.12$ U) values.

## Discussion

In assessing relationships between intrauterine 'asphyxia' and subsequent child development, the assessment of 'asphyxia' remains a major problem in the clinical setting. If oxygen tensions have indeed been measured, it is perfectly reasonable to refer to hypoxia. In almost all human studies, however, other indicators have been the basis for inferring that 'hypoxia' or 'asphyxia' has occurred. Limitations of these inferences should therefore be acknowledged.

Delayed onset of spontaneous respiration [11] and/or persisting low Apgar scores [17] as indices of severe asphyxia are related to neonatal death or brain damage in the surviving infant. This is especially likely if resuscitation attempts fail for prolonged periods of time [11,17].

In AFD term infants no long term neurological sequelae as a result of abruptio

placentae, placenta previa and prolapse of the cord [12] and of low umbilical artery buffer base values [10] have as yet been found. In selected groups of term infants – including growth retarded ones – with various signs of intrapartum and neonatal distress and signs of neonatal neurological abnormalities, it has been shown that approximately 30% of surviving infants have neurological sequelae [1,3]. Finer et al. [3] found, however, no significant relationship between any of over 100 obstetrical antepartum or intrapartum variables and outcome. Only a 5 min Apgar score < 3 was related to sequelae at later age. It remains therefore uncertain if these abnormalities are due to 'asphyxia' during fetal life or that the respiratory delay is rather a symptom shown by infants who may be in a poor condition for other reasons and therefore is merely a marker of other defective reactions to various insults [13].

As regards the neonatal neurological condition, earlier reports from the Groningen Perinatal Project showed that in preterm and growth-retarded infants acidaemia at birth doubles the incidence of neonatal neurological abnormalities [5]. In a study of 75 AFD term infants born in vertex presentation Stolte et al. [18] also found a significant relationship between $PH_{ua}$ values and neonatal neurological optimality scores; a $PH_{ua}$ of 7.25 (the mean value) or more was in 32 out of 33 cases associated with neurological optimality (i.e., a reduction of the score by 6 points or less). The same authors found no such relation in vaginally delivered AFD breech infants ($n = 48$) [6].

In the present larger study in AFD term infants only a slight relation between pH at birth and neonatal neurological condition was found. In the total study group the highest predictive value was found for $\Delta pH_{m\text{-}ua}$, but with $\Delta$pH values only 0.8% of variance in the NNOS was explained. In the low risk group the highest predictive value was also found for $\Delta$pH values, explaining 4% of variance.

The slightly stronger relation between acidaemia at birth and neonatal neurological morbidity in this group might be due to the absence of other obscuring obstetrical pathology. Another explanation might be that the incidence of maternal acidaemia was lower in the low risk group than in the total group. In that case fetal acidaemia would more likely be of fetal origin. The low predictive values imply that factors other than those associated with acidaemia are causative in a large majority of AFD infants with neurological abnormality.

Even though according to normal criteria a considerable number of infants was born acidaemic, severe acidaemia at birth was present in only a few cases. Assessment of the effect of extreme acidaemia, therefore, is not possible in this study. Of the 9 infants born with a $pH_{ua} < 7.00$, 5 were classified as suspect, but none as abnormal. As regards the neurological diagnosis only a relation between pH or $\Delta$pH and a suspect condition could be demonstrated. Neonatal neurological abnormality was not related to pH or $\Delta$pH and was found equally distributed in all pH ranges, but the group of abnormal infants was small compared to the size of the normal and suspect infants' groups. After correction for neurological asymmetries of peripheral origin (e.g. paresis of the 6th cranial nerve; $n = 6$), which are caused by a direct mechanical birth trauma, the results remained the same. Apparently acidaemia in this group of infants is only related to neurological symptoms but not to syndromes. This is in contrast to preterm and growth retarded infants [5]. The weak relationship

we found was only expressed in a small increase of minor neurological signs, which have a fair chance of recovery in subsequent weeks or months. Factors other than those associated with acidaemia must be responsible for causing neonatal neurological abnormalities. One may think of congenital or antepartum acquired brain damage, the latter possibly caused by infections, self-administered medication or transient unrecognized antenatal periods of hypoxia. The observation of Fricker et al. [4] of a partially decerebrated AFD term infant born with normal blood gases, in whom a transitory occlusion of the umbilical cord had probably occurred in utero, supports the idea that antenatal hypoxia can play a role in causing brain damage.

An indication that other factors besides those associated with acidaemia are responsible for neurological abnormality can be found in the low risk group. In this group of infants born after a low risk pregnancy and delivery, the incidence of neonatal neurological abnormality was less than half of that in the total group (1.5% versus 3.7%), despite a similar birthweight and pH distribution. The selection of the study group therefore is an important variable in studying the relationship between acidaemia at birth and neonatal neurological morbidity. Lievaart and de Jong [9] found a higher incidence of acidaemia at birth and of neonatal neurological morbidity in a group of infants delivered at home by midwives as compared to a small, strictly selected hospital population. In light of the foregoing, the differences in neurological morbidity might just as well be explained by the selection of the patient group, as by the differences in medical care as suggested by the authors. The absence of neurological morbidity in their hospital population is in contrast to the present findings in the low risk group.

In the present investigation a large variation in maternal pH values was found (range 7.10 to 7.55). Maternal pH, however, was not related to neonatal neurological morbidity. In agreement with observations of others [2,16] it was found that umbilical cord pH is related to maternal pH at birth. It has been suggested that correction for this influence, by using the $\Delta$pH mother-fetus, results in a better measure of the infants' condition at birth [16]. The results of our study support this view, as $\Delta pH_{m\text{-}ua}$ best predicted the neonatal neurological optimality score, even though the predicted value was very low.

Because of the specific relation between maternal and umbilical pH, calculation of a maternal–fetal nomogram (Fig. 4) would theoretically seem useful. However, the incidence of suspect infants was only increased in the lowest percentile zones and this approach, at least in the AFD term infants' group, seemed to be no better than that of using non-corrected $\Delta$pH. In preterm and growth retarded infants in whom acidaemia plays a more important role in the causation of neurological abnormality [5], this approach might prove to be advantageous.

Some investigators consider the base-deficit gradient between mother and fetus ($\Delta BD_{m\text{-}f}$) a more practical method of discriminating between a fetal hypoxic acidaemia of endogeneous origin and maternal infusion acidaemia [2,16]. However, in this study no significant correlation between $\Delta$BD and the neonatal neurological condition was found (explained variance in NNOS in the total study group 0.23%). It can be concluded that, with regard to AFD term infants,

(1) a normal umbilical pH at birth does not guarantee a normal neonatal neurologi-

cal condition. In contrast, most of the neurologically suspect and abnormal neonates had normal pH values.
(2) No evidence was found in this AFD term infants' group that neonatal neurological abnormality was related to umbilical pH or to maternal–fetal ΔpH values.
(3) Minor neonatal neurological dysfunction is related to maternal–fetal ΔpH and to a lesser degree to umbilical pH values alone. With all measurements, however, the relation, although statistically significant, was weak.
(4) Umbilical arterial or venous pH, and maternal–fetal ΔpH *alone* cannot be used as predictors of neonatal neurology.

**Acknowledgements**

The authors are most grateful for critical reading and many suggestions made by Dr. J.G. Aarnoudse and Dr. M.J. O'Brien. Mrs. A. Olinga gave technical assistance. The Groningen Perinatal Project was supported by the Praeventiefonds and the Prinses Beatrixfonds.

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*Chapter 5*

# Apgar score, meconium and acidaemia at birth in relation to neonatal neurological morbidity in term infants

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**Summary.** The relation between Apgar score, meconium and acidaemia at birth and neonatal neurological morbidity was investigated in 805 vaginally born term infants whose birthweight was appropriate-for-dates (AFD). Presence or absence of meconium stained amniotic fluid was not related to the neonatal neurological condition. The 1-min and 3-min Apgar scores and the umbilical artery pH were related, but the variances explained in neonatal neurological optimality score were very low (0·9 and 0·5% respectively). Combination of Apgar score and pH slightly increased these percentages to 1·5. The highest frequency of neurologically deviant infants was, on the other hand, found in the group with a normal pH but low Apgar score. It is concluded that in AFD term infants nowadays the predictive value of a low Apgar score, acidaemia at birth and/or presence of meconium for the neonatal neurological morbidity is poor. Most neonatal neurological abnormalities must be due to other factors.

Hypoxia at birth can be recognized by low Apgar scores and is often associated with low pH values in umbilical cord blood. Meconium stained amniotic fluid is also considered to be an indicator of hypoxia. There are only a few reports in the literature concerning the effects of hypoxia on neonatal brain function, which is an important predictor of subsequent developmental abnormalities (Touwen 1981). We have previously shown that acidaemia at birth bears only a limited relation to the neonatal neurological condition in term infants whose birthweight was appropriate-for-dates (AFD) (Dijxhoorn *et al.* 1985). Until now there have been no comparable studies dealing with the relation between Apgar score and neonatal neurological condition. Whether cord blood gas measurements provide more valuable prognostic indications than Apgar scores, therefore, is still an unresolved question (Sykes *et al.* 1982). Several studies have shown a relation between Apgar scores and neurological development at a later age (Drage *et al.* 1966; Nelson & Ellenberg 1981). It has been shown that the prognosis is poorer if both acidaemia and low Apgar scores were present at birth (Litschgi *et al.* 1974). Comparable, although less convincing, data have been published with regard to the presence of meconium stained amniotic fluid (Nelson & Broman 1977). In the present study the relation of Apgar scores, umbilical pH values and presence or absence of meconium stained amniotic fluid, alone and in

*British Journal of Obstetrics and Gynaecology* March 1986, Vol. 93, pp. 217–222

**Table 1.** Selection criteria for the 'low risk' group ($n$ = 205)

| |
|---|
| No admission to hospital during pregnancy |
| No meconium stained amniotic fluid |
| No drugs given during labour |
| Duration of second stage of labour <60 min |
| Spontaneous vaginal delivery in vertex position |
| No congenital malformations |
| Antenatal obstetric optimality score of ⩾45* |

* The total 'obstetric optimality score' comprises 74 items relating to antenatal, intrapartum and immediate postnatal condition (Touwen *et al.* 1980); the antenatal part comprises 55 items; suboptimality was arbitralily defined as a score of ⩽44.

combination, with neonatal neurological morbidity is investigated. The study is restricted to AFD infants born vaginally at term.

## Patients and methods

The study group consisted of 805 AFD infants, born vaginally after 37 weeks gestation between 1975 and 1978. They are part of a birth cohort of 3162 infants who were examined neurologically during the neonatal period (Groningen Perinatal Project). The 805 infants were selected because complete data on maternal and umbilical blood gas values at birth were present. They were representative for the total group of 2499 AFD term infants (Dijxhoorn *et al.* 1985). From the group of 805 infants a 'low-risk' subgroup of 205 infants was selected, consisting only of infants born after a low-risk pregnancy and delivery. This was done to minimize the influence of other obstetric complications on neonatal neurological morbidity. The criteria for this selection are shown in Table 1.

The condition of the infants at birth was assessed by the Apgar scores at 1 and 3 min. An Apgar score of ⩽6 was considered to be low. Blood was aspirated from the umbilical artery and vein and from the maternal cubital vein for blood gas analysis directly after birth. The presence or absence of meconium stained amniotic fluid at the time of rupture of the membranes was noted. No distinction was made between early or late passage and thin or thick meconium. In accordance with the definition, in the low-risk group none of the infants had meconium stained amniotic fluid. In studying the relation between meconium staining and neonatal neurological morbidity, pregnancies with breech presentation were excluded as meconium passage in this group is usually due to compression and not to hypoxia.

A standardized neurological examination, as described by Prechtl (1977), was performed on the fourth or fifth day of life. The neonatal neurological condition was classified using a qualitative and quantitative approach. The qualitative approach entailed assigning each infant to one of three diagnostic categories: normal, suspect, abnormal. An infant was considered abnormal if one or more of the following neurological syndromes were present: hyper- or hypokinesia, hyper- or hypotonia, hemisyndrome, apathy syndrome, hyperexcitability syndrome. An infant was classified as suspect if only isolated symptoms were present, but no

**Table 2.** Relation of the 1- and 3-min Apgar score with the neonatal neurological condition

| | | | Neonatal neurological diagnostic category | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | | Normal | | Suspect | | Abnormal | | |
| Apgar score | $n$ | (%) | $n$ | (%) | $n$ | (%) | $n$ | (%) | NNOS median |
| 1-min* | | | | | | | | | |
| 1–3 | 6 | (1) | 2 | (33) | 4 | (67) | | | 52·5 |
| 4–6 | 51 | (6) | 32 | (63) | 14 | (27) | 5 | (10) | 53·4 |
| 7–10 | 746 | (93) | 583 | (78) | 138 | (19) | 25 | (3) | 55·3 |
| 3-min† | | | | | | | | | |
| 4–6 | 8 | (1) | 3 | (37) | 4 | (50) | 1 | (13) | 50·5 |
| 7–10 | 795 | (99) | 614 | (77) | 152 | (19) | 29 | (4) | 55·2 |
| Total | 803 | (100) | 617 | (77) | 156 | (19) | 30 | (4) | 55·2 |

Analysis of variance: * $F_{2,801} = 6{\cdot}08 - P < 0{\cdot}005$, and † $F_{1,801} = 6{\cdot}96 - P < 0{\cdot}01$.
NNOS, Neonatal neurological optimality score (Touwen *et al.* 1980).

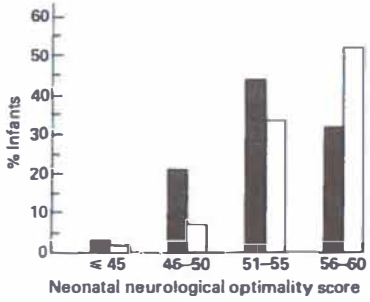


**Fig. 1.** Distribution of infants with a low (▨1–6) and high (□7–10) 1-min Apgar score in relation to the neonatal neurological optimality score.

defined syndromes. Another way of quantifying the neurological findings was the optimality concept as described by Prechtl (1980). This entailed defining an optimal range for 60 representative neurological items. Each infant obtained a neonatal neurological optimality score (NNOS), consisting of its items falling within the optimal range. This approach is quite different from the qualitative one, which is based on the 'normal-abnormal' concept. There is, however, a considerable overlap, whereby the interquartile ranges of the NNOS are 44–50 in abnormal infants, 49–54 in the suspect category and 54–58 in normal infants (Touwen *et al.* 1980). In the present study group of AFD term infants the median NNOS was 55 and the 10th centile 50 (Dijxhoorn *et al.* 1985). Details of both classifications have been published

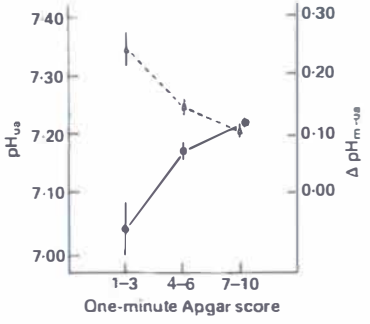


**Fig. 2.** Mean (± SEM) pH$_{ua}$ (umbilical artery pH, ●) and pH$_{m-ua}$ (maternal-umbilical artery pH, Δ) in three groups of infants with 1-min Apgar scores of 1–3, 4–6 and 7–10.

elsewhere (Jurgens-van der Zee *et al.* 1979; Touwen *et al.* 1980).

Statistical analysis used Student's *t*-test, analysis of variance and $\chi^2$. The relation of different indices of hypoxia and NNOS was studied, using the multiple regression analysis and was expressed as explained variance. In the Tables and Figures data are divided in subgroups for clearer presentation.

## Results

### *Total group*

In the total group of infants 7% had a low 1-min Apgar score and 1% had a low 3-min Apgar score. With both classifications of the neurological findings a significant relation between Apgar score and neonatal neurology was found (Table 2 and Fig. 1). However, only 0·9% of the variance in NNOS was explained by both the 1-min and 3-min Apgar scores.

Only six infants had a 1-min Apgar score of ≤3. They were equally distributed in the NNOS ranges 46–50, 51–55 and 56–60. This distribution therefore did not differ much from that of the total group with a 1-min Apgar score of ≤6.

The 1-min Apgar score was clearly related to both pH$_{ua}$ (umbilical artery pH) and $\Delta pH_{m-ua}$ (maternal-umbilical artery pH) (Fig. 2, Student's *t*-test $P < 0{\cdot}001$).

The correlation coefficients ($r$), however, were low (+0·21 for pH$_{ua}$ and −0·16 for $\Delta pH_{m-ua}$). An association between a low 1-min Apgar score and neonatal neurological deviance (suspect and abnormal diagnostic category and median NNOS values) was present at all pH ranges (Table 3). Surprisingly the highest frequency of suspect and abnormal infants as well as the lowest median NNOS was found in the category with a normal pH but low Apgar score. The percentage of explained variance in NNOS nearly doubled by the combination of Apgar score and one of the pH variables (1·5%).

Meconium-stained amniotic fluid was present in 18·5% of infants with a low 1-min Apgar score compared with 7·8% of those with a high score $\chi^2 = 8{\cdot}61$; d.f. = 1, $P < 0{\cdot}005$). The presence or absence of meconium was not related to the neonatal neurological condition (Table 4) or to either of the pH variables. It did not increase the percentage of explained variance in NNOS as found for Apgar scores or pH values alone.

Table 3. Relation between umbilical artery pH, 1-min Apgar score and the neonatal neurological condition

| Umbilical artery pH | 1-min Apgar score | *n* | Neonatal neurological diagnostic category: Normal (%) | Suspect (%) | Abnormal (%) | NNOS median |
|---|---|---|---|---|---|---|
| ≤7·10 | 1–6 | 17 | 71 | 29 | 0 | 54·0 |
| | 7–10 | 69 | 77 | 22 | 1 | 55·3 |
| | Total | 86 | 76 | 23 | 1 | 55·2 |
| 7·11–7·19 | 1–6 | 21 | 67 | 23 | 10 | 53·9 |
| | 7–10 | 191 | 73 | 22 | 5 | 55·2 |
| | Total | 212 | 73 | 22 | 5 | 55·1 |
| ≥7·20 | 1–6 | 19 | 42 | 42 | 16 | 52·0 |
| | 7–10 | 486 | 80 | 17 | 3 | 55·4 |
| | Total | 505 | 79 | 18 | 3 | 55·3 |

NNOS, Neonatal neurological optimality score (Touwen *et al.* 1980).

### *'Low-risk' group*

In the low-risk group no relation was found between Apgar score and neonatal neurological condition. In part this may be due to the small number of low 1-min Apgar scores (3%) and to the absence of low 3-min Apgar scores. The 1-min Apgar score in combination with one of the pH variables did not increase the percentage of explained variance in NNOS as found for pH alone (Dijxhoorn *et al.* 1985).

## Discussion

Hypoxia at birth is usually defined as low Apgar score and/or a low umbilical blood pH. The presence of meconium stained amniotic fluid is used as an additional indicator. Perinatal hypoxia may cause brain injury (Addy 1982), but its role in producing long-term neurological impairment should not be overestimated, as most hypoxia babies who are neurologically abnormal recover completely soon after birth (Nelson & Ellenberg 1981; Scott 1976). The incidence of neurological handicaps depends on the duration and severity of the hypoxic event (Low *et al.* 1977) and on other risk factors such as intrauterine growth retardation (Huisjes *et al.* 1980; Dweck *et al.* 1974) and preterm birth (Zippel *et al.* 1972).

In the present study the relation between hypoxia at birth and the neonatal neurological condition was investigated. Long-term neurological outcome as an index of the quality of obstetric care is of only limited value, as the effects of interval conditions on the one hand and compensatory mechanisms on the other can obscure relations found at a later age (Touwen 1981).

In this group of AFD term infants only a weak relation between Apgar scores and neonatal neurology was found. In part this may be due to the low incidence of very low Apgar scores (≤3). Assessment of the predictive value of very low Apgar scores, therefore, is not possible in this

Table 4. Relation of meconium stained amniotic fluid with the neonatal neurological condition (breech presentations are excluded)

| | Total *n* | (%) | Neonatal neurological diagnostic category: Normal *n* | (%) | Suspect *n* | (%) | Abnormal *n* | (%) | NNOS median |
|---|---|---|---|---|---|---|---|---|---|
| Meconium present | 66 | (9) | 51 | (77) | 13 | (20) | 2 | (3) | 55·4 |
| Meconium absent | 697 | (91) | 544 | (78) | 129 | (19) | 24 | (3) | 55·2 |
| Total | 763 | (100) | 595 | (78) | 142 | (19) | 26 | (3) | 55·2 |

NNOS, Neonatal neurological optimality score (Touwen *et al.* 1980).

study. Of the six infants with a 1-min Apgar score between 1 and 3, four were classified as suspect, but none as abnormal. In the same group of 805 infants an almost identically low relation was found between umbilical cord and maternal acid-base values at birth and neonatal neurological condition (Dijxhoorn *et al.* 1985). The variance explained in NNOS was only 0·5% for $pH_{ua}$ and 0·8% for $\Delta pH_{m-ua}$. Neurological abnormality was not related to pH variables at all, nor was the base-deficit gradient between mother and fetus related to the neonatal neurological condition.

These low relations may be due to the fact that with modern management, including intensive monitoring during labour and intensive neonatal treatment of hypoxia at birth, the incidence of prolonged hypoxia, during labour as well as after birth, is low. This is illustrated by the fact that only a few infants were born severely acidaemic or had a low Apgar score 3-min after birth. With a persisting low Apgar score, which may indicate on the one hand a severe birth hypoxia and on the other hand inadequate resuscitation, it has been shown that the incidence of neurological sequelae increases strikingly. Nelson & Ellenberg (1981), for instance, found that in AFD infants the incidence of cerebral palsy increased from 1·5% in infants with a 1-min Apgar score of ≤3, to 4·7% in infants with such a score after 5 min and to 57·1% in infants with a score of ≤3, 20 min after birth.

According to Litschgi *et al.* (1974) the highest incidence of hypoxia brain damage can be found when both a low Apgar score and acidaemia are present at birth. Combination of these indices in the present study indeed almost doubled the predictive value with respect to neonatal neurological outcome (NNOS); the percentage of explained variance remained, however, very low (1·5%). Unexpectedly the highest incidence of neurologically suspect and abnormal infants as well as the lowest median NNOS was found in infants with a low 1-min Apgar score and a normal $pH_{ua}$. These data suggest that factors other than hypoxia are involved. The findings lend support to the suggestion made in the follow-up study of the 1970 British Birth Survey, that a low Apgar score is a marker of defective reactions to various other insults, rather than an indicator of hypoxia (Peters *et al.* 1984).

Our results do not support the suggestions made by Sykes *et al.* (1982), that cord blood measurements might provide more valuable prognostic indications than do Apgar scores, at least in AFD term infants. The low correlation found between Apgar score and umbilical cord pH is, on the other hand, in agreement with the findings of these authors. Both measurements have to be considered as separate entities. Acidaemia is likely to reflect hypoxia during birth; low Apgar scores may reflect hypoxia, but may also be due to a variety of other reasons.

Meconium staining of the amniotic fluid has also been the subject of extensive studies, especially because of its possible significance as a sign of fetal distress/hypoxia. Results from the NCPP study (Nelson & Broman 1977) showed that the presence of meconium was associated with an increased incidence of severe neurological handicaps at a later age. Our results show no relation between the presence or absence of meconium and the neonatal neurological condition in AFD term infants. Neither could we confirm the findings of Starks (1980) who found that umbilical cord pH values in a meconium group were significantly lower than those in a non-meconium group. The reason for the lack of correlation between meconium and the neonatal neurological condition might be that the presence of meconium stained amniotic fluid was always an indication for continuous FHR monitoring, often for fetal micro-blood-gas analysis, and in the event of fetal distress for immediate delivery.

It can be concluded, that in AFD term infants with adequate monitoring and resuscitation facilities, the predictive value of a low Apgar score, acidaemia at birth and/or presence of meconium for the neonatal neurological morbidity is poor. Most neonatal neurological abnormalities could not be attributed to one of these indices, and hypoxia thus defined therefore seems not to be a major causative factor. With severe and/or prolonged hypoxia different relations have been reported, but in general there is a tendency to overestimate the risk of hypoxia at birth in the causation of handicap (Paneth & Fox 1983). We fully agree with the statement made by Niswander (1981) 'Measuring the fetal condition during the perinatal period must be continued, but we should not fool ourselves by insisting that we can avoid most brain damage by avoiding perinatal asphyxia'.

**Acknowledgments**

The authors are most grateful for critical reading

and many suggestions made by Dr M. J. O'Brien. Mrs A. Olinga gave technical assistance. The Groningen Perinatal Project was supported by the Praeventiefonds and the Prinses Beatrixfonds.

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*Received 29 April 1985*
*Accepted 5 August 1985.*

*Chapter 6*

# APGAR SCORE, MECONIUM AND ACIDAEMIA AT BIRTH IN SMALL-FOR-DATES INFANTS BORN AT TERM AND THEIR RELATION TO NEONATAL NEUROLOGICAL MORBIDITY

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Summary.

Neonatal neurological morbidity was studied in relation to Apgar score, meconium stained amniotic fluid and acidaemia at birth in 247 small-for-dates (SFD) maturely born infants. SFD infants and especially the severely SFD infants and those delivered abdominally, showed higher incidences of neurological morbidity, acidaemia and meconium stained amniotic fluid than appropriate-for-dates (AFD) controls. The examined indicators of asphyxia at birth showed slightly higher correlation coefficients with the Neonatal Neurological Optimality Score (NNOS) in SFD, than in AFD term infants. However, the percentage of explained variance was low, except in the abdominally delivered group (n=23). In the latter group poor neurological outcome was restricted to 14 infants who showed signs of fetal hypoxaemia (decelerative fetal heart rate (FHR) patterns). In 11 of them FHR decelerations occurred antepartum. These FHR abnormalities appear to be better predictors for the neonatal neurological outcome than indicators of asphyxia at birth.

## INTRODUCTION

Mature small-for-dates (SFD) infants show an increased incidence of neurological abnormalities not only in the neonatal period (Huisjes et al. 1980) but also at a later age (Fitzhardinge & Stevens 1972; Neligan et

al. 1976). Various suggestions have been made about the aetiological background of these long-term sequelae. On the one hand a relation between late neurological impairment and the severity of intrauterine growth delay has been demonstrated (Neligan et al. 1976), reflecting perhaps the reduction of brain weight (Larroche & Korn 1977) and brain cell number (Winick & Rosso 1969). On the other hand it has been suggested that the increased incidence of asphyxia (Low et al. 1978) might contribute to the incidence and severity of late handicap in these mature SFD infants (Dweck et al. 1974).

To make rational decisions about the type of intervention in pregnancies complicated by intrauterine growth delay it is important to answer the question, as to what contribution the associated hazard of intrapartum hypoxaemia/acidaemia makes to the incidence and severity of neurological handicap and what would be the "residuum of handicap" when hypoxic insults are prevented (Tayler 1984). In an earlier study in appropriate-for-dates (AFD) full-term infants we found a very low correlation between indices of asphyxia (such as low Apgar scores, umbilical acidaemia and meconium stained amniotic fluid) and the neonatal neurological condition (Dijxhoorn et al. 1986). However, in a combined group of term- and preterm SFD infants acidaemia nearly doubled the incidence of neonatal neurological abnormality (Huisjes et al. 1980). No studies have as yet been published on the relation between Apgar scores alone or in combination with umbilical cord acid-base values on the one hand and neonatal neurology on the other in SFD infants born at term. Such studies would nevertheless be of interest since the added impact of prematurity on the central nervous system is excluded.

In the present study the relation between indices of asphyxia at birth and the neonatal neurological condition were investigated in severely and moderately SFD infants born at term, delivered vaginally or by Caesarean section (CS).

The data are compared with those of earlier studies of AFD term infants (Dijxhoorn et al. 1985 and 1986).

## PATIENTS AND METHODS

Subjects were selected from the data base of the Groningen Perinatal Project, containing pre- and perinatal data on 3162 children from con-

secutive singleton pregnancies, all surviving the neonatal period. 2991 of these infants were born after 37 completed weeks of gestation and of these 374 (12.5%) were below the tenth centile for birth weight according to the Amsterdam growth charts (Kloosterman 1970). In 247 of these 374 infants umbilical artery pH($pH_{ua}$) values were available; of these 23 were delivered by CS and 224 vaginally. In the latter group 178 had a birth weight between the 2.3 and 10th centile (moderate SFD) and 46 below the 2.3 centile (severe SFD). A complete blood gas analyses (including $pCO_2$ and Base Excess = BE of blood from the umbilical artery and maternal vein) was available in 130 of the SFD infants (53%). Two control groups of AFD term born infants were selected from the Perinatal Project cohort. One included 805 vaginally born infants selected only because a complete acid-base status of mother and infant taken directly after birth was available. This group was representative of the total group of AFD term infants, as has been described previously (Dijxhoorn et al. 1985). The second control group consisted of 82 infants delivered by CS with known $pH_{ua}$ values.

After delivery the newborn infants were assessed by Apgar scores at one and three minutes and by taking blood from the umbilical artery and from the maternal cubital vein for blood gas analysis directly after birth. The presence or absence of meconium in the amniotic fluid at the time of rupture of the membranes was noted.

The results of a standardized neurological examination (Prechtl 1977) were expressed in a neurological classification (normal, suspect or abnormal) and in a neonatal neurological optimality score (NNOS; range 0-60) (Touwen et al. 1980 and Dijxhoorn et al. 1985).

Statistical analysis: The Student's t test, the Mann-Whitney U test, the chi-square test (Table I and IV) and the analysis of variance (for mean $pH_{ua}$ values) or the Kruskall-Wallis test (for median three minute Apgar scores; Table II) were used. Multiple regression analysis was used to examine the effects of acid-base variables, Apgar scores, and meconium on the NNOS as the dependant variable (Table III). The squared multiple correlation coefficient ($R^2$) indicates the proportion of variance in NNOS explained by the indicators of asphyxia.

## RESULTS

SFD infants scored less than AFD controls on all but one of the indices

Table I. Indices of neonatal morbidity in various study groups of infants born at term according to birth weight (small-for-dates = SFD; appropriate-for-dates = AFD) and birth route (vaginally or by Caesarean section).

| | | | VAGINAL DELIVERY | | CAESAREAN SECTION | |
|---|---|---|---|---|---|---|
| | severe SFD (n=46) | moderate SFD (n=178) | total SFD (n=224) | total AFD (n=805) | SFD (n=23) | AFD (n=82) |
| neonatal neurological condition: | | | | | | |
| normal (%) | 40 | 68 | 62 | 77 | 48 | 70 |
| suspect (%) | 36 ---**--- | 26 | 28 ---*--- | 19 | 35 ---*--- | 23 |
| abnormal (%) | 24 | 6 | 10 | 4 | 17 | 7 |
| NNOS (median) | 52.9 ---**--- | 55.2 | 54.8 ---*--- | 55.2 | 53.5 | 54.5 |
| 1 min Apgar score median | 8.4 | 8.7 | 8.7 | 8.7 | 7.8 | 7.8 |
| $pH_{ua}$ mean (SD) | 7.17 (0.09) -*-- | 7.19 (0.10) | 7.19 (0.10) -**- | 7.22 (0.09) | 7.18 (0.09) | 7.19 (0.10) |
| $\Delta pH_{m-ua}$ mean (SD) | 0.16 (0.10) | 0.14 (0.10) | 0.15 (0.10) -**- | 0.12 (0.08) | 0.15 (0.10) | 0.15 (0.09) |

NNOS - Neonatal Neurological Optimality Score (Touwen et al. 1980)
*p <0.05; **p < 0.01

of neonatal morbidity (neonatal neurological diagnosis, optimality score $pH_{ua}$ and $\Delta pH_{m-ua}$). For the Apgar scores no significant differences were found. Severely SFD infants did worse than moderately SFD infants. Both in the study and control groups the poorest outcome was found in infants delivered abdominally (Table I).

Table II. Median one-minute Apgar score and mean $pH_{ua}$ by neonatal neurological classification in appropriate-for-dates (AFD) and small-for-dates (SFD) born infants at term (vag = vaginally; CS = Caesarean section).

| | Groups (n) | Neonatal Neurological Diagnostic Category | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | normal | (n) | suspect | (n) | abnormal | (n) | |
| one-min Apgar score | AFD, vag (803) | 8.7 | (617) | 8.4 | (156) | 8.4 | (30) | $p < 0.01$ |
| | SFD, vag (224) | 8.7 | (139) | 8.5 | (63) | 8.1 | (22) | $p < 0.005$ |
| | AFD, CS (79) | 8.0 | (54) | 7.0 | (19) | 6.0 | (6) | NS |
| | SFD, CS (23) | 8.5 | (11) | 7.0 | (8) | 5.5 | (4) | NS |
| $pH_{ua}$ | AFD, vag (805) | 7.22 | (619) | 7.20 | (156) | 7.22 | (30) | $p < 0.025$ |
| | SFD, vag (224) | 7.19 | (139) | 7.18 | (63) | 7.19 | (22) | NS |
| | AFD, CS (82) | 7.20 | (56) | 7.19 | (20) | 7.10 | (6) | $p < 0.05$ |
| | SFD, CS (23) | 7.23 | (11) | 7.12 | (8) | 7.17 | (4) | $p < 0.025$ |

Table III. Percentages of variance (squared multiple correlation coefficients- $R^2$) in neonatal neurological optimality score (NNOS) explained by some clinical incidences of asphyxia at birth (BE- base excess, $\Delta$BE and $\Delta$pH-differences between maternal- and umbilical artery BE- and pH respectively, AS 1' and AS 3'- one- and three minute Apgar scores respectively) according to birth route and birth weight (SFD-small-for-dates and AFD-appropriate-for-dates).

| | VAGINALLY BORN | | | | CAESAREAN SECTION | |
|---|---|---|---|---|---|---|
| | severe SFD (n=46) | moderate SFD (n=178) | total SFD (n=224) | total AFD (n=805) | SFD (n=23) | AFD (n=82) |
| Best single variable | BE | AS1' | AS1' | AS1' | $\Delta$ BE | $\Delta$ BE |
| $R^2$ | 15.4 | 2.5$^{+}$ | 3.8$^{++}$ | 0.9$^{++}$ | 84$^{++}$ | 9 |
| Combination | AS1'+BE | AS1'+$\Delta$ BE | AS1'+$\Delta$ BE | AS1'+ $\Delta$pH | AS3'+ $\Delta$BE | AS1'+ $\Delta$BE |
| $R^2$ | 20.3 | 7.0$^{+}$ | 5.6$^{+}$ | 1.5$^{++}$ | 93$^{++}$ | 22 |
| All variables (*) | | | | | | |
| $R^2$ | 22.1 | 7.1$^{+}$ | 7.1$^{+}$ | 2.0$^{+}$ | 93$^{++}$ | 26 |

(*) one- and three-minute Apgar score, $pH_{ua}$, $\Delta$ pH, BE, $\Delta$ BE and meconium; + $p < 0.05$; ++ $p < 0.025$

In the vaginally born infants, both the SFD and the AFD, the median values of one-minute Apgar scores, but not the mean $pH_{ua}$, declined with the impairment in neurological diagnostic classification (normal, suspect, abnormal). Both the one-minute Apgar score and the $pH_{ua}$ declined in the two categories of infants born abdominally (Table II). This was, however, only significant for the $pH_{ua}$.

The indices of asphyxia contributed more to the explanation of variance in NNOS in the SFD infants than in the control group of AFD infants (Table III). However, the percentage of explained variance was low in all subgroups, except in the SFD-CS group. This group of 23 SFD infants born by CS was therefore further analysed.

"Late" fetal heart rate (FHR) decelerations had been present in 14 of the 23 cases (11 antepartum and 3 intrapartum). Poor neurological outcome was restricted to this subgroup and growth retardation was in general more severe among these 14 infants (Table IV). Within this

Table IV. Differences in birth weight, pH variables and neurological outcome in small-for-dates infants delivered by Caesarean section, with (n=14) and without (n=9) "late" fetal heart rate (FHR) decelerations; p <0.01 for measured parameters.

| | birth weight (mean ± SD) | $pH_{ua}$ (mean ± SD) | $\Delta pH_{m-ua}$ (mean ± SD) | Neonatal neurological diagnostic category normal n | suspect n | abnormal n | NNOS median |
|---|---|---|---|---|---|---|---|
| late decelerations | 2271 ± 404 | 7.14 ± 0.09 | 0.22 ± 0.07 | 3 | 7 | 4 | 51.6 |
| normal FHR pattern | 2601 ± 313 | 7.25 ± 0.05 | 0.12 ± 0.08 | 8 | 1 | 0 | 56.0 |

NNOS: Neonatal Neurological Optimality Score (Touwen et al. 1980)

subgroup no relation between $pH_{ua}$ and NNOS was found (figure 1). The occurence of antepartum "late" FHR decelerations seems therefore to be more important than the actual $pH_{ua}$ values at delivery, taken into account the absence of such decelerations in the vaginally delivered SFD infants.

In the SFD infants born vaginally the occurrence of meconium stained amniotic fluid (15.7%) was significantly more frequent than in the AFD group (8.6%) ( $\chi^2$=9.0; p <0.01). No significant relationships, however, were found between the presence or absence of meconium and the Apgar scores or pH variables, nor with the neonatal neurological condition.

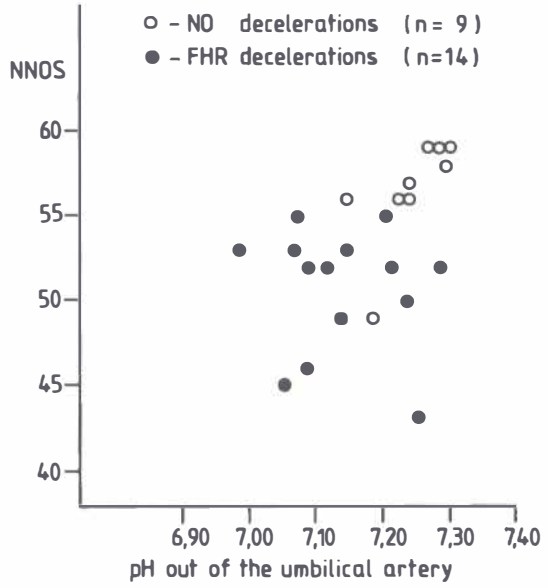


Figure 1. Relationship between pH out of the umbilical artery ($pH_{ua}$) and the Neonatal Neurological Optimality Score (NNOS) in 23 small-for-dates infants born by Caesarean section ($r = +041$; $p < 0.05$). 14 infants had "late" fetal heart rate (FHR) decelerations ($r = -0.13$; p-value not significant) and nine had no FHR abnormalities ($r = +067$; $p < 0.05$).

## DISCUSSION

Even when born at term, SFD infants, especially those with a birth weight below the 2.3 centile, show more neurological abnormalities than AFD infants. Within the frequently used definition of SFD, based on birth weight for gestation, it is not possible to differentiate between babies which are genetically small and those who are abnormally small as a result of a disease process (congenital infection, drug exposure, reduced supply caused by chronic uteroplacental insufficiency). Severe growth retardation is probably the result from chronic uteroplacental insufficiency. Because fetal asphyxia is often the terminal event in this sequence, it is not surprising that in the below 2.3 subgroup the highest association between indicators of "asphyxia" and the neonatal neurological condition is found.

From the literature it is evident that in term SFD infants not only short term morbidity but also late sequelae are increased. Studies at four to seven years of age (Fitzhardinge & Stevens 1972; Neligan et al. 1976) established low incidences of cerebral palsy, other major neurological deficits and mental retardation but a fairly high incidence of "minimal cerebral dysfunction" (speech and language problems, minor neurologic findings, school failures etc). Preliminary data from the Groningen Perinatal Project show a similar tendency (Touwen 1985). The more prolonged the period of growth retardation (Harvey et al. 1982) and the more severe growth delay (Neligan et al. 1976) the less likely the growth deficit was to be completely recoverable and the more it was found to be associated with neurological abnormalities (Wallis et al. 1977).

In preterm SFD infants the incidence of neurological abnormalities in the neonatal period (Huisjes et al. 1980) and at a later age (Drillien et al. 1980), has been reported to be higher than in term SFD infants. This may be due to the prematurity at birth, but also because the process of growth retardation in such children is likely to have begun earlier in pregnancy. In order to separate clearly those two groups in the present study only data on term SFD infants are given.

The poorer neurodevelopmental outcome in SFD infants can be explained by chronic nutritional deprivation of the brain (Gross et al. 1978) or by damage caused by asphyxia (Marriage & Davies 1977). Morphological findings in growth retarded infants (Dobbing 1974) and in animal models (Bedi 1984) show a smaller brain size, fewer cells, deficits in synapse-to-neurone ratios, reduced dendritic growth etc, rather than distinct neuropathological varieties of neonatal hypoxic-ischemic encephalopathy, as can be found after asphyxia (Kreusser & Volpe 1984).

The present data in SFD infants born at term indicate only a small contribution of intrapartum asphyxia, as signalled by Apgar scores and blood gas measurements to neonatal neurological morbidity. In those SFD infants born by CS a much stronger effect of prenatal fetal heart rate (FHR) abnormalities on neonatal neurology is found. "Late" FHR decelerations are thought to indicate fetal hypoxaemia (Meyers et al. 1973; Bekedam & Visser 1984). From growth retarded fetal sheep it is known that with a reduced supply line, both oxygen and glucose uptake diminish at a similar rate (Robinson et al. 1985). The resulting chronic hypoxaemia and hypoglycaemia were shown to be present for a pro-

longed period before acidaemia developed. In the present study the cases with "late" FHR decelerations probably represent such a pre-existing chronic metabolic deprivation and their occurrence appears to be more important than the actual condition at birth. In the present CS study group a so called "terminal" FHR pattern -indicative of fetal acidaemia (Visser et al. 1980)- was never found antenatally. Acidaemia ($pH_{ua}$ < 7.15; n=9) occurred only in cases in which the mothers were allowed to go into labour and long lasting acidaemia was therefore unlikely to have been present.

Severely SFD infants appear more vulnerable to hypoxia than moderately growth retarded infants: the percentage of variance in NNOS explained by the combined indicators of asphyxia was three times as high in the former than in the latter group (22% versus 7%). However, a squared multiple correlation coefficient of 0.22 is still low and in this small subgroup (N=46) was not statistically significant. The effect of severe asphyxia could not be studied because only 12 of the 247 SFD term born infants with a known $pH_{ua}$ had a $pH_{ua}$ below 7.00. Seven of these were neurologically suspect and one abnormal in the neonatal period. Ten of these infants could be neurologically examined at 6 years of age and only two showed a minor neurological dysfunction at that age. In the severely SFD infants BE and $\Delta$ BE were better related with neonatal neurological outcome than pH and $\Delta$ pH. This is in contrast to what was found in AFD term infants (Dijxhoorn et al. 1985). Because in severe growth retardation a metabolic acidaemia mostly develops due to anaerobic metabolism, these acid-base indicators can best be used in SFD infants to estimate the fetal and/or neonatal condition.

Of the total group of 247 SFD infants born at term with a known $pH_{ua}$ six were neurologically abnormal at four to six years of age (Hadders-Algra 1984). These six infants all belonged to the subgroup of 26 infants who were diagnosed as abnormal during the neontal period. Two of the six were acidaemic at birth ($pH_{ua}$=7.06 ) but they were also the most severely growth retarded ones.

It can be concluded that although these observations do not definitely indicate a proximate perinatal cause for neurological damage in SFD mature infants, they do reduce the likelihood that intrapartum "asphyxia" was the primary factor operating. Prolonged nutritional deprivation resulting in severe growth retardation, especially if associated with early signs of fetal hypoxaemia, seems to be more important

with respect to neonatal neurological outcome than indicators of "asphyxia" determined at birth. Delivery should take place before prenatal signs of hypoxaemia occur. Changes in umbilical artery and fetal aortic velocity wave forms, indicative of an increased placental vascular resistance, usually precede "late" FHR decelerations by approximately one to three weeks (Hernandez et al. 1984). With this new technique delivery before the occurrence of hypoxaemia may prove benificial in selected cases.

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*Chapter 7*

# APGAR SCORE, MECONIUM AND ACIDAEMIA AT BIRTH IN RELATION TO THE NEONATAL NEUROLOGICAL MORBIDITY. A COMPARISON BETWEEN APPROPRIATE-FOR-DATES AND SMALL-FOR-DATES FULLTERM AND PRETERM INFANTS

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SUMMARY

In 2220 infants the influence of gestational age, growth retardation and asphyxia at birth on neonatal neurological outcome was studied. Age and weight at birth appeared to be more important than asphyxia variables. At all ages poorest outcome was found in the growth retarded infants. The best correlation between asphyxia variables and neurological morbidity was found in the small-for-dates (SFD) preterm infants: more than 50% of variance in neurological outcome was explained by the combination of several asphyxia variables. Correlations were poorer in appropriate-for-dates (AFD) preterm infants and in SFD term infants and hardly present in AFD term infants. As in the SFD term group also in the SFD preterm infants the best correlation was found between antepartum fetal heart rate decelerations and neurological outcome, indicating that chronic hypoxaemia and malnutrition is more important than the actual condition at birth. Follow-up data of infants born preterm suggest that chronic hypoxaemia and/or acidaemia at birth might well have contributed to neurological abnormalities found at four years of age.

## INTRODUCTION

A high incidence of neonatal neurological abnormalities are found in preterm infants, especially in those born growth retarded (Huisjes et al. 1980; Westgren et al. 1984). Several studies also showed an increased incidence of asphyxia at birth (acidaemia, low Apgar scores) in these groups (Low et al. 1981; Westgren et al. 1982; Goldenberg et al. 1984). Intrapartum acidaemia has been shown to be associated with an almost 50% increase in neurological abnormalities in the neonatal period and at two year follow-up, as compared to non-acidaemic preterm infants (Westgren et al. 1984). These data suggest a high vulnerability of the premature brain to hypoxia. Other authors, however, could not confirm these findings in very premature infants (26-30 wks of gestation) (Shennan et al. 1985).

In appropriate-for-dates (AFD) term infants we showed that the relationship between acidaemia at birth with or without low Apgar scores and neonatal neurological morbidity was poor (Dijxhoorn et al. 1985; 1986a). In small-for-dates (SFD) term infants (Dijxhoorn et al. 1986b) this association was only slightly stronger, with the highest correlation seen in the most severely growth retarded infants. "Late" fetal heart rate (FHR) decelerations, antenatally or during labour, predicted neonatal neurological morbidity better than the umbilical cord arterial pH ($pH_{ua}$).

The interrelationship between asphyxia at birth, the duration of pregnancy, intrauterine growth and the neurological condition of the newborn is the subject of the present study. Furthermore, the impact of asphyxia at birth on the neonatal neurological condition is examined in AFD and SFD infants born prematurily. These data are compared with those previously found in term infants (Dijxhoorn et al. 1985; 1986a; 1986b).

## PATIENTS AND METHODS

The total study group comprises 2220 singleton live born infants with a known umbilical artery pH ($pH_{ua}$) born between June 30 1975 and July 1 1978 at the Department of Obstetrics, University Hospital Groningen, the Netherlands.

All infants survived the perinatal period and were examined neuro-

logically using the standardized neurological examination technique according to Prechtl (1977). The neurological examination of the preterm infants (born before 37 completed weeks of gestation; n = 126) took place in the 40th postmenstrual week and the same neurological criteria were used as in full-term infants (born after 37 completed weeks; n = 2094). This design was considered to be justified, as standardized neonatal examination techniques for preterm infants are not available. Moreover, in the absence of serious neonatal complications, the rate of maturation of the central nervous system is comparable intra- and extra-uterinely (Touwen 1980). The neonatal neurological condition was classified as normal, suspect or abnormal and was also expressed in a neonatal neurological optimality score (NNOS, range 0-60). Details of both procedures have been published previously (Jurgens-van der Zee et al. 1979; Touwen et al. 1980).

At delivery, the acid-base status was measured in the umbilical artery in the clamped cord and in the maternal cubital vein. In the previously studied 805 AFD term infants all feto-maternal blood gas variables were known (Dijxhoorn et al. 1985; 1986a). The present cases were selected on the presence of $pH_{ua}$ data only. In approximately 90% of these cases $\Delta\ pH_{m-ua}$ values and in 50% $\Delta\ BE_{m-ua}$ values (the difference between maternal venous pH or BE and $pH_{ua}$ or $BE_{ua}$ respectively) were also present. The Apgar scores were determined at one and three minutes after birth. Infants born prematurily were placed in an incubator for transportation to the neonatal intensive care unit. In the pediatric ward the baby was extensively examined (general examination and assessment of the gestational age according to Farr et al (1966). Infants were considered to be SFD if their birth weight, corrected for sex, parity and height of the mother, was below the 10th percentile (Kloosterman 1970).

## Statistical analysis

Analysis of variance (for mean values) and the Kruskall-Wallistest (for median values) were conducted to compare the differences of mean $pH_{ua}$ and median three minute Apgar scores in the three neonatal neurological diagnostic categories (Table I) and to compare the mean and median values of several parameters in three different fetal heart rate pattern categories (Table IV). A simple (Table II) and a multiple regression

Table I. Mean $pH_{ua}$ and median three-minute Apgar score by neonatal neurological classification in a total group of appropriate-for-dates (AFD) and small-for-dates (SFD) infants and those born at term or preterm

| | | | | Neonatal Neurological Diagnostic Category | | | |
|---|---|---|---|---|---|---|---|
| | | | n | normal | suspect | abnormal | p value |
| $pH_{ua}$ | AFD | total group | 1928 | 7.21 | 7.20 | 7.20 | p - NS |
| | | at term | 1835 | 7.21 | 7.20 | 7.19 | p < 0.05 |
| | | preterm | 93 | 7.21 | 7.20 | 7.24 | p - NS |
| | SFD | total group | 292 | 7.20 | 7.17 | 7.16 | p < 0.025 |
| | | at term | 259 | 7.20 | 7.18 | 7.19 | p - NS |
| | | preterm | 33 | 7.20 | 7.12 | 7.06 | p < 0.05 |
| | AFD + SFD | | 2220 | 7.21 | 7.19 | 7.19 | p < 0.001 |
| three minute Apgar score | AFD | total group | 1928 | 9.6 | 9.3 | 8.9 | p < 0.001 |
| | | at term | 1835 | 9.6 | 9.4 | 8.9 | p < 0.01 |
| | | preterm | 93 | 8.4 | 9.1 | 8.0 | p - NS |
| | SFD | total group | 292 | 9.5 | 9.1 | 8.5 | p < 0.001 |
| | | at term | 259 | 9.6 | 9.2 | 9.0 | p < 0.01 |
| | | preterm | 33 | 8.5 | 8.3 | 6.7 | p - NS |
| | AFD + SFD | | 2220 | 9.6 | 9.3 | 8.7 | p < 0.001 |

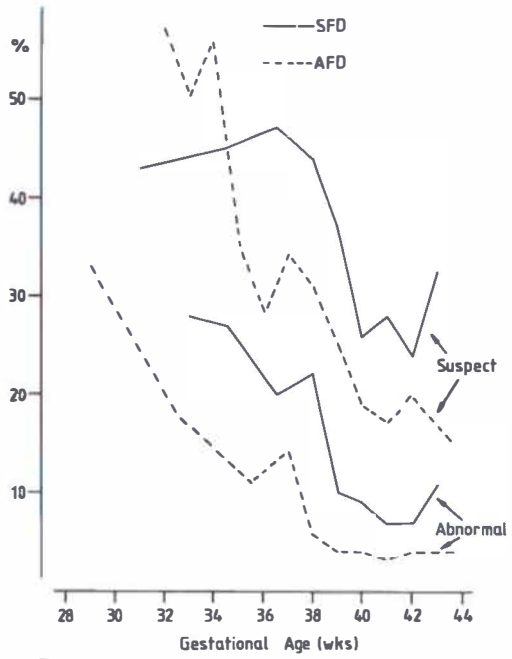


Figure 1. The relationship between gestational age and incidence of neonatal neurologically abnormal and suspect infants. AFD = appropriate-for-dates; SFD = small-for-dates.

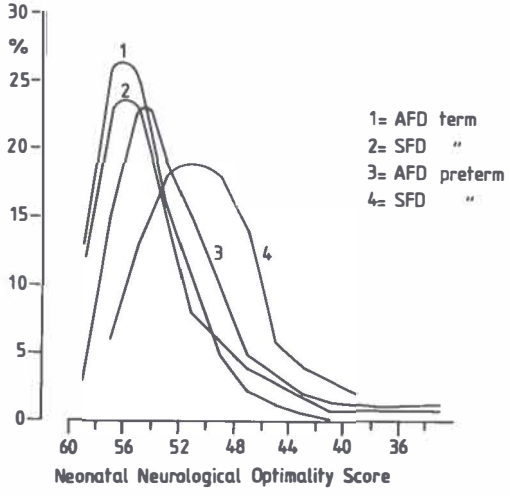


Figure 2. Distribution of the neonatal neurological optimality score in AFD (appropriate-for-dates) and SFD (small-for-dates) term- and preterm infants.

analysis (Table III) was used to examine the effects of various independent variables on the NNOS as dependent variable (the percentage of explained variance in the NNOS is the squared multiple correlation coefficient).

## RESULTS

There was an inverse relationship between gestational age and neonatal neurological morbidity ("suspect" and "abnormal" infants). The poorest outcome was found at all ages in the SFD infants (Fig. 1). The distribution of the NNOS was displaced and deviated to lower scores in cases of intrauterine growth retardation (IUGR), preterm birth and especially when both conditions were combined (Fig. 2).
In the AFD infants gestational age did not influence the median $pH_{ua}$ value (Fig. 3). In the SFD group the median $pH_{ua}$ was clearly related

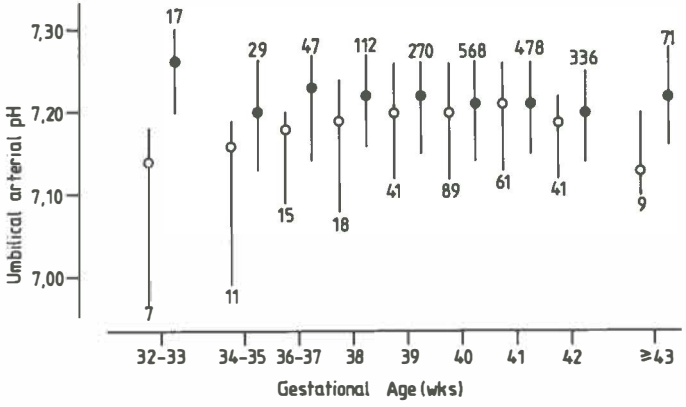


Figure 3. Relationship between gestational age and umbilical arterial pH at birth (medians and quartiles). The number of observations at various gestational ages are indicated on the graphs. ● = appropriate-for-dates and o = small-for-dates.

to the gestational age. The lowest values were seen in preterm and postterm (after 42 completed weeks of gestation) infants. A clear relationship was found between the one-minute Apgar score and the duration of gestation in SFD infants and also to a lesser degree in AFD infants (Fig. 4).

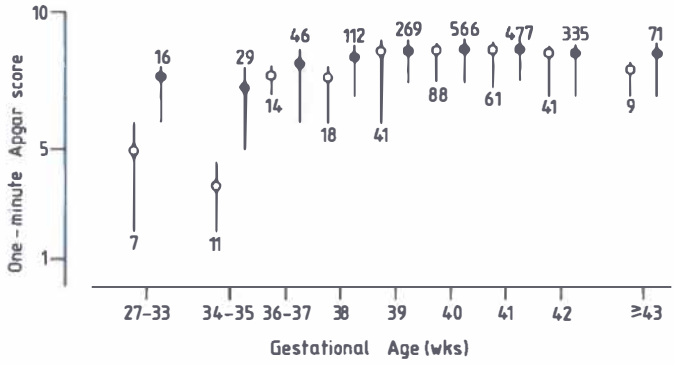


Figure 4. Relationship between gestational age and one-minute Apgar score (medians and quartiles). The number of observations at various gestational ages are indicated on the graphs. ● = appropriate-for-dates and o = small-for-dates.

In the term AFD and the preterm SFD infants the mean $pH_{ua}$ was significantly lower when the neurological classification was "suspect" or "abnormal", but the difference was only substantial in the preterm SFD infants. The median three-minute Apgar scores were only lower in neurologically deviant infants when they were born at term (Table I). Asphyxia had an important effect on the NNOS in SFD preterm infants only: in the multiple regression analysis over 50% of the variance was explained by all asphyxia indicators taken together. All other correla-

Tabel II. Simple regression analysis with the NNOS as the dependent variable and the "asphyxia" parameters as independent variables in various study groups. (Percentages of explained variance in NNOS).

| "asphyxia" variable | Total group AFD + SFD n = 2220 | Born at term AFD n = 1835 | Born at term SFD n = 259 | Born preterm AFD n = 93 | Born preterm SFD n = 23 |
|---|---|---|---|---|---|
| $pH_{ua}$ | 0.1 | 0.0 | 0.5 | 0.0 | 5.2 |
| $BE_{ua}$ | 0.0 | 0.1 | 0.3 | 4.8 | 10.2 |
| $\Delta pH_{m-ua}$ | 0.1 | 0.0 | 1.1 | 1.4 | 8.9 |
| $\Delta BE_{m-ua}$ | 0.0 | 0.1 | 0.2 | 5.0 | 9.9 |
| meconium | 0.1 | 0.1 | 0.1 | 2.1 | 0.0 |
| one-minute Apgar-score | 2.2*** | 1.1*** | 6.0*** | 0.3 | 10.9 |
| three-minute Apgar-score | 2.4*** | 1.3*** | 4.9*** | 0.0 | 14.5* |
| all asphyxia variables | 2.5** | 1.4* | 9.5 | 18.3 | 54.3* |

NNOS = Neonatal neurological optimality score; AFD = appropriate-for-dates; SFD = small-for-dates; * = $p < 0.05$; ** = $p < 0.005$; *** = $p < 0.001$

tions between asphyxia and NNOS were either small or not statistically significant (Table II).

In the total study group the indices of asphyxia did not contribute much in explaining the variance in the NNOS when the gestational age and birth weight had already been taken into account (Table III). In

Table III. Stepwise multiple regression analysis with the NNOS as the dependent variable in various study groups. The increase in the percentage of explained variance in NNOS after the asphyxia variables entered the analysis (step 2) is shown in brackets.

| Predictor variable | Total group AFD + SFD n = 2220 | Born at term AFD n = 1835 | Born at term SFD n = 259 | Born preterm AFD n = 93 | Born preterm SFD n = 93 |
|---|---|---|---|---|---|
| (1) gestational age and birth weight | 3.3*** | 0.8*** | 13.3*** | 8.1* | 12.3 |
| (2) asphyxia variables | 4.0*** (0.7) | 2.0** (1.2) | 17.1*** (3.8) | 15.8 (7.7) | 59.1 (46.8) |

NNOS = Neonatal neurological optimality score; AFD = appropriate-for-dates; SFD = small-for-dates; * = $p < 0.05$; ** = $p < 0.005$; *** = $p < 0.001$

the subgroups the additional predictive value of these indices was better, again with the highest increase in the SFD preterm infants.

As the highest association was found between the NNOS and the parameters of asphyxia in SFD preterm infants, this group was further analyzed. Seven of the 33 infants had shown the presence of a so-called "terminal" FHR pattern (Visser et al. 1980) in the antenatal period and all were delivered by elective Caesarean section (CS). Fourteen had a so-called "decelerative" FHR pattern (on ten occasions already present antenatally), 11 of these infants were born by CS and three vaginally. The remaining 12 had a "normal" FHR pattern antenatally and during labour and all were born vaginally (Table IV). Significantly different mean $pH_{ua}$ values, median Apgar scores and neonatal neurological outcomes were found in the three FHR pattern categories: the best outcome occurred in the infants with a "normal" FHR pattern, the poorest in those with a "terminal" pattern. All eight neurologically abnormal infants had an abnormal FHR pattern and in seven this had already been present before labour. Four of these eight infants had a normal $pH_{ua}$ at birth ($pH_{ua} \geq 7.15$), which might indicate that the presence of antenatal FHR abnormalities are more important than the

Table IV. Differences in birth weight, $pH_{ua}$ (mean ± SD), gestational age, Apgar scores (median) and neurological outcome in preterm small-for-dates infants with "terminal", "decelerative" and "normal" fetal heart rate patterns.

| Variable | "terminal" n = 7 | "decelerative" n = 14 | "normal" n = 12 | significance |
|---|---|---|---|---|
| birth weight (g) | 1307 ± 137 | 1436 ± 502 | 1739 ± 325 | $p < 0.025$ |
| gestational age (wks) | 34.3 | 35.5 | 36.0 | NS |
| $pH_{ual}$ | 6.99 ± 0.15 | 7.16 ± 0.10 | 7.18 ± 0.07 | $p < 0.005$ |
| AS $1^1$ | 3.0 | 6.7 | 8.2 | $p < 0.005$ |
| AS $3^1$ | 7.2 | 8.5 | 9.6 | $p < 0.025$ |
| NNOS | 48.5 | 50.7 | 53.5 | $p < 0.05$ |
| neonatal neurological diagnostic category: | | | | |
| normal (n) | 0 | 4 | 7 | $x^2 = 10.75$; $p < 0.05$ |
| suspect (n) | 3 | 6 | 5 | |
| abnormal (n) | 4 | 4 | 0 | |
| follow-up: | | | | |
| abnormal at 4 to 6 years (n) | 2 | 2 | 0 | |

$NNOS_1$ = Neonatal Neurological Optimality Score; AS $1^1$ = one-minute Apgar score; AS $3^1$ = three-minute Apgar score

actual pH value at birth.

At four to six years of age, eight of the 126 premature infants (6.3%) turned out to be neurologically abnormal, as compared to 20 (15.9%) in the neonatal period (Hadders-Algra et al. 1986). Four of these eight infants had been AFD (4/93 = 4.3%) and four SFD (4/33 = 12.1%). Five of the eight cases had had a $pH_{ua} < 7.10$; three of them even had a $pH_{ua}$ below 7.00.

## DISCUSSION

These data clearly show the influence of the duration of pregnancy and the occurrence of intrauterine growth retardation on neonatal neurological functioning. These two variables appeared to be more important with respect to neurological morbidity than "asphyxia at birth". However, this only held true when the total study group or when the subgroup born after 37 weeks were analyzed (Table III). In the AFD preterm infants the addition of the "asphyxia" variables to age at birth doubled the predictive value of the NNOS, whereas in the SFD preterm infants the explained variance increased from 12 to nearly 60%. In other words, in the latter group the condition at birth seemed to be a better predictor of neonatal neurological brain functioning than the actual

duration of pregnancy (28-37 weeks).

This does not necessarily mean that "acute" asphyxia at birth in preterm growth retarded infants is the most important cause of neurological morbidity. On the contrary, from Table IV it can be seen that the best correlation was found for fetal heart rate patterns which were mainly obtained antenatally (17 out of 21 abnormal patterns). A "decelerative" antepartum FHR pattern is indicative of hypoxaemia (Bekedam and Visser 1984) and a "terminal" pattern is indicative of acidaemia found at elective CS (Visser et al. 1980). So the infants who were neurologically abnormal had already shown signs of hypoxaemia during the antenatal period. This is more likely to be indicative of "chronic" asphyxia than of "acute" asphyxia at birth. From experimental studies in growth retarded fetal sheep it is known that the uptake of oxygen and glucose diminish at a similar rate and that hypoxaemia and hypoglycaemia may last for a rather long period of time before acidaemia develops (Robinson et al. 1985). Therefore, in our opinion, impairment of brain function in preterm growth retarded infants is more likely to be due to chronic malnutrition - including hypoxaemia - than to hypoxaemia alone. This reasoning can to a large extent be supported by the morphological findings in human growth retarded infants (Dobbing 1974) and in animal models (Bedi 1984) where a smaller brain size, fewer cells etc. are found, rather than distinct lesions as is often the case after (acute) asphyxia (Kreusser and Volpe 1984). Similar results, with respect to antepartum FHR patterns versus acidaemia at birth have been reported previously in SFD term infants (Dijxhoorn et al. 1986b).

The present data suggest that growth retarded fetuses should be delivered before antepartum signs of hypoxaemia appear. It may be possible to detect fetuses at risk for antepartum asphyxia by studying their umbilical artery velocity wave forms, as it is known that changes in these wave forms usually preceed the occurrence of decelerations (Trudinger et al. 1986). However, not enough is known about false-positive abnormal wave form patterns and delivering the baby even more prematurily may increase the risk of vital conditions, such as the respiratory distress syndrome (RDS), neonatal intracranial haemorrhage etc. Thus far the best option to prevent neurological handicap is to prevent growth retardation. In women with a poor obstetrical history, antiplatelet therapy seems to be promising (Beaufils et al. 1985).

In the AFD preterm infants the relationship between "asphyxia" vari-

ables and neonatal neurological morbidity was, although evident, less pronounced than in the SFD preterm group. As there is no reason to presume that chronic malnutrition/asphyxia had been present in the former group it is suggested that the effect on the neonatal neurological condition is mainly the result of more-or-less acute "asphyxia" during labour. Westgren et al. (1984) also observed in acidotic (fetal scalp pH less than 7.25), premature, mostly AFD infants significantly more neurologic abnormalities in the neonatal period and a higher rate of neurodevelopmental disabilities at the follow-up than non-acidotic infants of the same gestational age. On the bases of these data in AFD preterm infants it seems important that "asphyxia at birth" should be prevented.

An inverse relationship between the incidence of acidosis at birth and duration of pregnancy has been reported (Low et al. 1981; Westgren et al. 1982) and the suggestion was made that preterm labour per se is hypoxigenic. That this is not the case, has been shown by Kubli (1977) in an unselected preterm population and in the present study in AFD preterm infants.

The predictive value of acid-base variables and Apgar scores regarding the neurological condition may vary with gestational age. In term infants we previously found that the predictive value of the Apgar score was slightly better than that of the $pH_{ua}$ (Dijxhoorn et al. 1986a; see also Table I). The poorest outcome was found in infants with a normal pH but a low Apgar score. It was suggested that a low Apgar score is more a marker of defective reactions due to various other insults, rather than an indicator of hypoxia (Peters et al. 1984). In general the prognostic value of the blood gas variables in preterm infants is better than that of the Apgar scores. In contrast to what was found in AFD full term infants (Dijxhoorn et al. 1985), the $BE_{ua}$ and $\Delta BE_{m-ua}$ were slightly better related with neonatal neurological outcome than $pH_{ua}$ and $\Delta pH_{m-ua}$.

Follow-up data from the "Groningen Perinatal Project" showed that 6.3% (eight out of 126) of the infants born prematurily were neurologically abnormal at four years of age (Hadders-Algra et al. 1986). The incidence of neurological handicap seemed to be considerably higher in SFD compared to AFD preterm infants (four out of 33 versus four out of 93). Commey and Fitzhardinge (1979) also observed that the risk of cerebral palsy and/or neurological handicap at two years of age was

significantly higher in the SFD preterm group. This was not found when AFD and SFD infants of equal birth weight were examined without considering gestational age (Koops et al. 1978; Vohr et al. 1979). "Asphyxiated" SFD preterm infants appear to be at greater risk for major handicap during childhood than AFD preterm infants (Commey and Fitzhardinge 1979; Westgren et al. 1986). This is in agreement with our findings on neonatal neurological morbidity and the effects of "asphyxia" as shown in this paper. There were insufficient infants in this study to evaluate the effects of acidaemia at birth on later outcome in the AFD- and SFD preterm subgroups separately. Of the eight infants in the combined group who were abnormal at four years of age, five had been acidaemic ($pH_{ua} < 7.10$); three of them were severely acidaemic ($pH_{ua} < 7.00$) indicating that "asphyxia", whether chronic and associated with prolonged malnutrition or acute, might well have contributed to these abnormalities. The fact that all five infants had abnormal antepartum FHR patterns ("late" decelerations) stresses the danger of chronic hypoxaemia.

Acknowledgements

The authors are most grateful for statistical and technical assistance given by Dr V. Fidler and Mrs A. Olinga respectively.
The Groningen Perinatal Project was supported by the Praeventiefonds and the Prinses Beatrixfonds.

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*Chapter 8*

# THE EFFECT OF MATERNAL ALKALAEMIA AT BIRTH ON UMBILICAL ARTERY BLOOD GAS VALUES

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SUMMARY

The effect of maternal alkalaemia at birth on umbilical artery blood gas status was investigated in 951 vaginally born infants. In 805 appropriate-for-dates (AFD) term infants no adverse effects of maternal alkalaemia could be demonstrated. In 110 small-for-dates (SFD) term infants signs of developing metabolic acidaemia were found (subnormal pH, increase in $pCO_2$ and increase in $\Delta$BE-difference between maternal and umbilical artery BE). In 36 preterm infants mainly respiratory impairments were observed (increase in $pCO_2$ and decrease in $pO_2$). It seems that spontaneous maternal hyperventilation during labour, leading to alkalaemia at delivery, can better be avoided. This is especially applicable to SFD infants.

## INTRODUCTION

Maternal alkalaemia at birth is mostly the result of hyperventilation during parturition (1). There is continuing controversy in the literature about the potential adverse effects of maternal hyperventilation on the fetus (2, 3).

Investigations into the effects of hyperventilation in humans revealed that moderate shifts in maternal acid-base balance towards alkalaemia are reflected in the fetus or the infant at birth by an improvement in the acid-base status (4, 5). Some reports, however, provided evidence that maternal hyperventilation significantly reduces, rather than im-

proves the oxygen supply to the fetus (5, 6). In a few studies on humans (7, 8) even signs of an accompanying fetal metabolic acidosis were found; on the basis of this, it has been concluded that hyperventilation during labor can be hazardous to the fetus, particularly to those already in distress. Specific obstetrical risk populations which might suffer particularly from any decrease in uteroplacental blood flow as a result of maternal alkalaemia have not been recognized thus far.
The present study was undertaken to determine whether maternal hyperventilation at delivery has any particular effect on growth retarded (and possibly chronically stressed in utero) and/or preterm infants.

## PATIENTS AND METHODS

The total study group consisted of 951 singleton infants, born vaginally between 1975 and 1978 at the Groningen University Hospital. They form part of the 3162 infants born consecutively during that period, constituting the birth cohort of the Groningen Perinatal Project (9, 10). In all 951 infants a complete umbilical cord (vein and artery) and maternal blood gas analysis was available. Failure to obtain all blood gas variables (including $pO_2$, $pCO_2$ and Base Excess (BE)), did not introduce a selection bias (11). The infants born by Caesarean section were excluded because of the possibly unfavourable influences of general anaesthesia, ventilation etc. on the fetal acid-base status (4, 12).
The effect of maternal alkalaemia at birth on the umbilical acid-base status was investigated in three different subgroups; group 1: 805 appropriate-for-dates (AFD) infants (birthweight $\geq$ 10th percentile according to the Amsterdam growth charts (13)), born at term (after 37 completed weeks of gestation); group 2: 110 small-for-dates (SFD) infants (birthweight $<$10th percentile) born at term. This group could be increased to 223 infants if the criteria had only included the availability of maternal- and umbilical artery pH values; group 3: 36 AFD infants born prematurily ( $<$37 completed weeks of gestation). This group could be enlarged to 68 infants if only the pH values were available. The SFD preterm infants were not included in this study because too few had known maternal- and umbilical pH values (n = 11).
Maternal cubital vein blood samples were taken simultaneously with the umbilical artery samples, within five minutes after birth. The blood gas

analysis was carried out immediately after obtaining the sample, or, if delay was necessary, after keeping it on ice. The pH, $pCO_2$ and $pO_2$ values were analysed directly on an IL 313 digital pH blood gas analyzer and the BE value was calculated automatically.

Moderate alkalaemia at birth was arbitrarily defined as a maternal pH $\geq$7.41 (pH value above the 90th percentile of the total 951 cases) and severe maternal alkalaemia as a maternal pH $\geq$ 7.43 (above the 95th percentile). This selection was based on the maternal pH values, because alterations in the pH, rather than the $pCO_2$ values have been shown to be the most influential factor in placental vascular resistence (14).

In the statistical analyses student's test was applied to compare the differences between mean acid-base values.

## RESULTS

### Appropriate-for-dates term infants

In group 1 infants the umbilical artery acid-base changes followed those of their mothers, whereby higher umbilical artery pH ($pH_{ua}$) and BE ($BE_{ua}$) and lower $pCO_2$ ($pCO_{2ua}$) values were found in the alkalaemic cases (Table I). The increase in $pH_{ua}$ and decrease in $pCO_{2ua}$ values were less pronounced than in the maternal vein. This was reflected in a significant increase in the difference between maternal- and umbilical artery pH and $pCO_2$ values ($\Delta$pH and $\Delta$ $pCO_2$ respectively). However, the difference between maternal- and fetal BE values ($\Delta$ BE) remained constant. The mean $pO_{2ua}$ in the severely alkalaemic group (22 mmHg) was slightly, but not significantly ($p = 0.06$) lower than that in the control group (25 mmHg). A significant reduction in $pO_{2ua}$ (18 mmHg; $p < 0.05$) was only found with extremely low maternal $pCO_2$ values (< 22 mmHg).

### Small-for-dates term infants

In group 2 the increase in $pH_{ua}$ was only minimal in cases of moderate alkalaemia and actually absent in severe alkalaemia. Despite a clear decrease in maternal $pCO_2$ values, the $pCO_{2ua}$ values were higher than in the control group; this difference was statistically significant for

Table I. Comparison of mean umbilical artery blood gas and pH data for normal maternal pH values (control group) and maternal alkalaemia (moderate and severe) in the three study groups.

| | | | UMBILICAL ARTERY | | | DELTA VARIABLES | | |
|---|---|---|---|---|---|---|---|---|
| | | n (%) | pH | $pO_2$ mmHg | $pCO_2$ mmHg | BE | $\Delta$pH | $\Delta$ $pCO_2$ | $\Delta$ BE |
| group 1 AFD at term n = 805 | control group $pH_{mat}$ 7.30-7.36 | 378 (47) | 7.21 | 25 | 52 | -5.6 | 0.12 | 16 | 0.0 |
| | moderate alkalaemia $pH_{mat} \geq 7.41$ | 83 (10) | 7.28 *** | 23 | 50 * | -2.1 *** | 0.16 *** | 19 * | 0.0 |
| | severe alkalaemia $pH_{mat} \geq 7.43$ | 40 (5) | 7.29 | 22 | 49 | -2.1 | 0.17 | 19 | +0.6 |
| group 2 SFD at term n = 223 | control group $pH_{mat}$ 7.30-7.36 | 106 (48) | 7.19 | 23 | 52 | -6.4 * | 0.15 ** | 14 * | +0.8 |
| | moderate alkalaemia $pH_{mat} \geq 7.41$ | 21 (9) | 7.21 | 23 | 54 * | -3.7 | 0.21 ** | 20 * | +1.8 * |
| | severe alkalaemia $pH_{mat} \geq 7.43$ | 9 (4) | 7.19 | 21 | 58 | -4.8 | 0.25 | 25 | +3.4 |
| group 3 AFD premature n = 68 | control group $pH_{mat}$ 7.30-7.36 | 20 (29) | 7.20 * | 19 | 53 | -3.9 | 0.14 ** | 17 * | -1.6 |
| | moderate alkalaemia $pH_{mat} \geq 7.41$ | 22 (32) | 7.26 ** | 16 * | 55 * | -0.6 * | 0.20 ** | 21 *** | +1.7 * |
| | severe alkalaemia $pH_{mat} \geq 7.43$ | 12 (18) | 7.28 | 13 | 56 | -0.1 | 0.20 | 22 | +2.1 |

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

severe maternal alkalaemia (Table I). This is in contrast to the findings in group 1. As a consequence, the increases in $\Delta pH$ and $\Delta pCO_2$ were more profound in group 2 than in group 1. In group 2 the increase in $BE_{ua}$ with maternal alkalaemia was less than that in the maternal blood. The $\Delta BE$ increased significantly with severe maternal alkalaemia (Table I).

Infants born prematurely

In group 3 a relatively high percentage of women showed moderate- or severe alkalaemia at delivery (32% and 18% respectively). The $pH_{ua}$ changes followed those of the women with alkalaemia (Table I). The $pCO_{2ua}$ values on the other hand (as in group 2), were higher than those in the control group. The $BE_{ua}$ changes followed those of the alkalaemic women, but the negative $\Delta BE$ values in the control group were positive with maternal alkalaemia. The mean $pO_{2ua}$ was significantly lower in the alkalaemic than in the control group.

## DISCUSSION

These data clearly show that maternal alkalaemia at delivery, which is mostly the result of maternal hyperventilation during labor, is potentially hazardous for certain groups of fetuses. Signs of developing (metabolic) acidaemia were found in association with maternal alkalaemia, especially in SFD fetuses. It is suggested that these fetuses were often in borderline situations due to utero-placental insufficiency. The biochemical signs were no increase in $pH_{ua}$ simultaneously with the rise in maternal pH, hypercapnia instead of hypocapnia in the umbilical artery and increasing $\Delta BE$ values, indicating an accumulation of fixed acids etc. in the fetus (15).

The influence of maternal alkalaemia on umbilical artery blood gas and acid-base values was also evident in the premature infants. This group mainly had respiratory impairments (increase in $pCO_{2ua}$ and decrease in $pO_{2ua}$), with to a lesser degree also metabolic changes (increase in $\Delta BE$). However, the accumulation of fixed acids had not yet reached the degree of acidaemia, as normal $pH_{ua}$ values were found. In the AFD term infants adverse effects of maternal alkalaemia could not be demonstrated. Placental $CO_2$ transfer continued efficiently to the lowest levels

of maternal $pCO_2$, whereby decreases in maternal $pCO_2$ were relative to the decreases in $pCO_{2ua}$. The metabolic component ($\Delta$BE) remained constant. The small decrease in fetal $pO_2$ had not accumulated to a degree of oxygen debt sufficient to produce signs of developing (metabolic) acidaemia.

The reduction in oxygen supply to the fetus during maternal hyperventilation is thought to be the main cause of deviations in the fetal blood gas values. In the literature the following physiologic mechanisms have been suggested as being responsible for this decrease in fetal oxygenation. In animals maternal hyperventilation can cause a uterine arterial vasoconstriction which reduces uterine artery blood flow and subsequently compromises placental perfusion (12, 14, 16). Further, in experiments carried out under general anaesthesia a maternal hypotension (14, 16) and small reduction in cardiac output (17), especially when accompanied by the vena cava inferior syndrome, was observed. Both in animals (14) and in human placental perfusion experiments (18) a decrease in umbilical blood flow had been found. Finally maternal hyperventilation shifts the maternal oxyhemoglobin dissociation curve to the left, thereby increasing the affinity of maternal blood for oxygen, but decreasing the oxygen available to the fetus (14).

It is difficult to compare the data of studies on this subject because of the great variations in study design (human, animal, anaesthetized or not) and the use of different parameters to assess the fetal condition. In most human hyperventilation experiments acute respiratory alkalaemia was associated with an increase in fetal pH due to hypocapnia; the metabolic response, evaluated by estimating buffer base levels of maternal- and fetal blood, was minimal (5) or absent (4, 6). The decrease in umbilical saturation was limited because of the shift to the left of the fetal oxyhemoglobin dissociation curve. Prolonged hyperventilation, studied in most animal experiments, revealed on the other hand a progressive decrease in fetal $pO_2$ values and the development of a hypoxic metabolic acidosis (14, 16). In the few human studies (7, 8) in which signs of a fetal metabolic acidosis were found following hyperventilation, it was suggested that in some of these cases the maternal-fetal relationship was already compromised before hyperventilation started and that any decrease in blood flow occuring due to alkalosis might cause an unexpected decompensation and a depressed fetus (18). In animals there is convincing evidence that growth retarded fetuses

can be chronically hypoxaemic (19). In human SFD fetuses, often with marginally functioning placentae due to placental insufficiency, we think that maternal alkalaemia may cause further reductions in transplacental oxygen transfer.

In summary, the present data indicate that especially in growth retarded, but also in preterm infants, maternal alkalaemia at birth has a deleterious effect on the fetus. A cause-and-effect relationship appears to exist. Although definitive acidaemia in the umbilical cord ($pH_{ua} \leq 7.15$) was only found in association with maternal alkalaemia in a few infants (n = 4) the biochemical changes observed are indicative of developing (metabolic) acidaemia. It is clear that in these sometimes already chronically distressed fetuses an additional impairment in fetal oxygenation due to maternal alkalaemia can finally lead to actual metabolic acidaemia at birth.

"Willful" hyperventilation during labor in these "at risk" fetuses should therefore be avoided. These data also show that a subnormal (7.16 - 7.24) or normal ($\geq 7.25$) $pH_{ua}$ does not necessarily indicate the absence of significant hypoxia. In severe cases of maternal alkalaemia such pH values may be falsely high. The difference between maternal venous and umbilical artery pH ($\Delta pH$), preferably corrected with the help of a maternal-fetal pH nomogram (11), seems to be a better indicator of the actual condition of the fetus at birth.

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*Chapter 9*

# SUMMARY AND CONCLUSIONS

In the literature there appears to be little consensus as to how much of the "burden of neurological handicap in the community is attributable to birth asphyxia" (Paneth & Stark 1983). The etiology of perinatally related "brain damage" is much more complicated than would be suggested by the information from the media over the "blue-looking" baby at birth. The pathophysiology of "brain damage", when asphyxia at birth is involved, is a complex matter (Chapter 2). The value of Apgar scores, umbilical cord blood gas and acid-base status, meconium staining of the amniotic fluid, etcetera, as indices of asphyxia at birth is uncertain and their value as predictors of neurological outcome has been a disappointment (Chapter 2).

This investigation was undertaken in order to test the null hypothesis presented in the general introduction (Chapter 1) that "asphyxia at birth is a main cause of neonatal neurological dysfunction". The relationships between indices of asphyxia at birth and neonatal neurological findings are investigated in various study groups (Chapters 4, 5, 6 and 7). The reason to address neurological outcome in the newborn is extensively discussed in the methods section (Chapter 3). The study population was part of a birth cohort of 3162 infants who were examined neurologically during the neonatal period and who were born between June 30 1975 and July 1 1978 at the Department of Obstetrics, University Hospital Groningen, The Netherlands (Groningen Perinatal Project). The subjects were selected because (complete) data on maternal and umbilical blood gas variables were available. It has to be stressed, however, that the total birth cohort is not representative of all regional births, as it comprises a clinical population with, in the majority of cases a medical indication for a hospital delivery (it does not contain the population of Dutch home deliveries which are generally of low risk).

The neonatal neurological outcome of the total cohort is shown in Table 1. From this table it is clear that the incidence of neonatal neurological abnormality is increased in growth retarded and especially in preterm

Table I. Number and percentages of neonatal neurologically abnormal infants in various study groups

| | | NEUROLOGICALLY ABNORMAL | |
|---|---|---|---|
| | n | n | % |
| AFD term | 2658 | 104 | 3.9 |
| SFD term | 333 | 31 | 9.3 |
| Preterm | 171 | 26 | 15.2 |
| Total | 3162 | 161 | 5.1 |

infants (with or without growth retardation). This also held true when neurologically suspect infants and the neonatal neurological optimality score (NNOS) were taken into account (Chapter 7). However, it is clear that the majority of neonatally abnormal infants were born at term and were appropriate-for-dates.

With respect to the main hypothesis presented in the general introduction, it can be said that asphyxia at birth is indeed a contributive cause of neonatal neurological dysfunction, but is not a main cause. On the whole, neonatal neurological morbidity is higher among infants who experienced birth asphyxia as signalled by low Apgar scores and blood gas and acid-base abnormalities in the umbilical cord. The risk of neonatal neurological dysfunction associated with birth asphyxia per se must, however, not be overestimated as it depends on the cumulative effects of various circumstances which in themselves influence the occurrence of acidaemia, such as preterm birth, growth retardation, difficult labour, complicated pregnancy etcetera.

In AFD infants born vaginally at term (Chapter 4) acidaemia at birth was only found to be slightly related to neonatal neurological morbidity. This relationship was only present for (minor) neurological symptoms (suspect infants) and for the NNOS. However, the percentages of variance in NNOS explained by the blood gas variables were very low (< 1%). Neonatal neurological abnormality was not at all related to $pH_{ua}$ or to $\Delta pH_{m-ua}$ and was equally distributed over the pH ranges. Because of the specific relationship between maternal- and umbilical pH a corrected maternal-fetal pH nomogram was calculated. Although this approach is theoretically useful, it did not visibly improve the relationship with neurological outcome. Apparently, acidaemia at birth in this group of infants is only related to neurological symptoms, not to

syndromes. Comparable data were recently obtained in a follow-up study of AFD term infants who were born extremely acidaemic ($pH_{ua} \leq 7.00$). At the age of two and a half to nine years these infants did equally well as matched controls (Aarnoudse et al. 1985).

In the same group of AFD term infants as studied in Chapter 4, meconium stained amniotic fluid, as an indicator of asphyxia, was not at all related to neonatal neurological morbidity (Chapter 5). On the other hand, the one- and three-minute Apgar scores were related but the variance explained in NNOS was -again- very low (< 1%). A combination of the Apgar score with one of the pH variables increased this percentage to 1.5%. The highest incidences of neurologically suspect and abnormal infants, as well as the lowest median NNOS values, were found in infants with a low one-minute Apgar score but with a normal $pH_{ua}$. This unexpected finding suggests that factors other than hypoxia are involved and also that a low Apgar score is more a marker of defective reactions as a result of various other insults than an indicator of hypoxia. This suggestion was also made on the basis of the follow-up study of the 1970 British Birth Survey (Peters et al. 1984). In a "low risk" subgroup of AFD term infants (Chapter 4 and 5), which was created to examine the significance of asphyxia per se by eliminating additional variables possibly affecting the neonatal neurological condition, it could be seen that the data for pH and Apgar score variables did not noticably vary with obstetrical risk.

Thus, Chapters 4 and 5 bring us to the conclusion that asphyxia at birth was not responsible for evident neonatal neurological abnormalities in our population of AFD term infants. This implies that the causes could not be identified for the majority of neurologically abnormal infants (see Table 1), although they can probably be found among those discussed in Chapter 2. Recent literature (Sims et al. 1985; Paul et al. 1986; Mann 1986) indicates that central nervous system (CNS) injuries occurring prior to the labour process are not rare. Up until now many of the infants with such CNS injuries have probably been left with unexplained neurological handicaps. It is a challenge for modern obstetrics to identify these cases and develop methods for their prevention.

In SFD term infants (Chapter 6), especially if they were severely growth retarded and/or delivered abdominally, we found higher incidences of neonatal neurological morbidiy and asphyxia/hypoxia at birth than in the AFD term group. Severely SFD infants appeared to be more

vulnerable to hypoxia than moderately SFD infants. The percentage of variance in NNOS explained by the combined indicators of asphyxia was three times as high in the former group as in the latter (22% vs 7%). Although the figures are slightly higher than in AFD term infants, these low percentages in SFD term vaginally born infants still only indicate a small contribution of intrapartum asphyxia to neonatal neurological morbidity. In the SFD term infants delivered abdominally the combination of measured asphyxia variables explained 93% of the variance in NNOS. On the other hand, poor neurological outcome in these infants was restricted to those in whom "late" FHR decelerations (14/23 = 61%) had been present. It is suggested that these signs of fetal hypoxaemia, which were mostly present antenatally (79%), are more important with respect to neurological outcome than the commonly used indicators of asphyxia at birth. Similar data were obtained in the SFD infants born prematurely (Chapter 7). In this group heart rate decelerations (present in 80% of the cases antenatally) also correlated better with neurological outcome than the Apgar score and/or pH variables at birth. Impaired neurological functioning in these infants is therefore more likely to be due to "chronic" hypoxaemia (and malnutrition) than to "acute" asphyxia at birth. This reasoning is to a large extent supported by morphological findings in human growth retarded infants (Dobbing 1974) and in animal models (Bedi 1984) where a smaller brain size, fewer cells etcetera are found, rather than distinct lesions as is often the case after ("acute") asphyxia (Kreusser & Volpe 1984). Similar data with respect to antepartum FHR abnormalities have recently been published by Lorentz et al. (1986). These data suggest that growth retarded infants should preferably be delivered before antepartum signs of hypoxaemia occur. The benefits of prevenient intervention must, however, be weighed against the risks of premature delivery and the methods for early identification of fetuses at risk for intrauterine hypoxaemia (e.g. analysis of the umbilical artery velocity wave form) still have to be validated. Carefully controlled studies are necessary to answer these questions.

In AFD preterm infants a relationship between "asphyxia" (especially the pH) variables and neonatal neurological morbidiy was evident, although less pronounced than in the SFD preterm group (Chapter 7). On the basis of the data presented in this chapter it can be stated that it is essential to prevent asphyxia at birth as much as possible in

preterm AFD infants. In fact, this group was the only one in which a clear effect of birth asphyxia (thus excluding "chronic" hypoxaemia already present before birth) could be demonstrated. In contrast to the findings of others, preterm labour per se does not appear to be hypoxigenic.

For all 247 SFD term infants (Chapter 6) and all 126 preterm infants (Chapter 7) complete neurological follow-up data at four to six years of age were available (Hadders-Algra et al. 1986). In the former group two of the six infants who were neurologically abnormal at four to six years of age had been acidaemic at birth ($pH_{ua}$ < 7.10) and in the latter group five out of eight. This means that acidaemia was present at birth in 50% (n = 7) of the definitive neurologically abnormal infants (n = 14) in these at-risk groups. The fact that in six of these seven infants an abnormal fetal heart rate pattern had been present antenatally stresses the danger of "chronic" hypoxaemia.

The effect of maternal alkalaemia at birth (one of the possible maternal acid-base disturbances which may have an adverse effect on the fetus) on umbilical artery blood gas and acid-base status is investigated in Chapter 8. In AFD term infants no adverse effect on the fetus could be demonstrated, whereas in SFD term infants we found signs of developing (metabolic) acidaemia and in preterm infants signs of respiratory impairments.

## CONCLUSIONS

It is concluded that,

1. the majority of neonatal neurologically abnormal infants were appropriate-for-dates and born at term
2. "asphyxia at birth" is not a main causative factor of neurological abnormality in appropriate-for-dates term infants, at least not in this selected Dutch population
3. in growth retarded infants chronic malnutrition (including chronic hypoxaemia) appears to be more important with respect to neurological outcome than the actual condition at birth
4. "asphyxia at birth" is related to neurological impairment in preterm appropriate-for-dates infants.

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# SAMENVATTING

In de literatuur wordt verschillend gedacht over de vraag in hoeverre neurologische handicaps in een gemeenschap toe te schrijven zijn aan asfyxie tijdens de geboorte (Paneth en Starks 1983). De etiologie van in de perinatale periode opgelopen "hersenbeschadiging" is veel gecompliceerder dan wordt gesuggereerd door de informatie in de media over de "blauw uitziende" baby bij de geboorte en de pathophysiologie van "hersenbeschadiging", als gevolg van asfyxie tijdens de geboorte, is een gecompliceerde zaak (Hoofdstuk 2). De Apgar scores, de gas en zuur-base status van bloed uit de navelstreng, meconium in het vruchtwater, enzovoorts, als tekenen van asfyxie bij de geboorte, zijn onzekere factoren en hun voorspellende waarde voor de neurologische conditie (neonataal en op latere leeftijd) lijkt teleurstellend (Hoofdstuk 2).
Dit onderzoek werd verricht om de in de algemene inleiding (Hoofdstuk 1) gestelde nul hypothese te toetsen dat "asfyxie aanwezig bij de geboorte een hoofdoorzaak is van neonataal neurologisch dysfunctioneren". In verschillende studiegroepen is de relatie tussen tekenen van asfyxie bij de geboorte en de neonataal neurologische bevindingen nagegaan (Hoofdstukken 4, 5, 6 en 7). De reden waarom wij juist bij de pasgeborene de neurologische conditie bepaalden wordt uitvoerig besproken in het onderdeel methoden (Hoofdstuk 3). De studiegroep maakte deel uit van een geboortecohort van 3162 kinderen, geboren tussen 30 juni 1975 en 1 juli 1978 op de afdeling Obstetrie van het Academisch Ziekenhuis te Groningen, die gedurende de neonatale periode neurologisch werden onderzocht (Perinataal Project Groningen). Geselecteerd werden de gevallen waarvan de (complete) bloed-gasvariabelen van moeder en kind beschikbaar waren.
De neonataal-neurologische conditie in het totale cohort is weergegeven in Tabel 1. In deze Tabel is duidelijk te zien dat de incidentie van het neonataal neurologisch abnormaal zijn groter is bij groeivertraagde en in het bijzonder bij prematuur geboren kinderen (met of zonder foetale groeivertraging). Dit geldt overigens ook voor de incidentie van neurologisch-suspect zijn en voor de neonatale neurologische optimaliteitsscore (NNOS) (Hoofdstuk 7). Het is evenwel duidelijk dat de meeste neonataal abnormale kinderen à terme geboren zijn en niet groeivertraagd zijn.
Met betrekking tot de nulhypothese kan worden vastgesteld dat asfyxie

Table I. Aantallen en percentages van neonataal-neurologisch afwijkende kinderen in verschillende studiegroepen

| | | NEUROLOGISCH ABNORMAAL | |
|---|---|---|---|
| | N | n | % |
| niet groeivertraagd à terme | 2658 | 104 | 3.9 |
| wel groeivertraagd à terme | 333 | 31 | 9.3 |
| prematuur | 171 | 26 | 15.2 |
| totaal | 3162 | 161 | 5.1 |

bij de geboorte inderdaad oorzakelijk bijdraagt tot neonataal neurologisch dysfunctioneren, maar dat het niet een van de hoofdoorzaken ervan is (Hoofdstukken 4, 5, 6 en 7). Over het geheel genomen is de neurologische morbiditeit in de neonatale periode hoger bij asfyktisch geboren kinderen (abnormale navelstreng bloed-gas en zuur-base waarden en lage Apgar scores). Het risico van neonataal neurologisch dysfunctioneren, samenhangend met asfyxie bij de geboorte, moet evenwel niet worden overschat, aangezien dit risico afhankelijk is van het cumulatieve effect van enkele bijkomstige factoren, zoals premature geboorte, foetale groeivertraging, moeilijke bevalling, zwangerschapscomplicaties, enzovoorts, op zichzelf reeds het voorkomen van acidemie beïnvloeden.
In niet groeivertraagde à terme vaginaal geboren kinderen (Hoofdstuk 4) was acidemie bij de geboorte slechts in geringe mate gerelateerd aan de neonataal neurologische morbiditeit. Deze relatie bestond alleen voor (lichte) neurologische afwijkingen (suspecte kinderen) en voor de NNOS. De percentages variantie in NNOS die door de bloed-gasvariabelen werden verklaard waren evenwel erg laag (< 1%). Het neonataal neurologisch abnormaal zijn vertoonde geen verband met de arteriële navelstreng-pH ($pH_{na}$) of met het verschil tussen de maternale veneuze en de arteriële navelstreng-pH ($\Delta\ pH_{m-na}$) en was gelijkmatig verdeeld over de totale pH verdeling. Omdat er een specifieke relatie lijkt te bestaan tussen de maternale- en de navelstreng-pH werd een gecorrigeerd maternaal-foetaal pH nomogram berekend. Hoewel deze benadering theoretisch gezien van belang zou kunnen zijn, bleek dit de relatie met de neonataal neurologische conditie niet duidelijk te verbeteren. In deze groepen van kinderen is acidemie bij de geboorte blijkbaar alleen gerelateerd aan neurologische symptomen en niet aan syndromen. Recentelijk werden vergelijkbare data verkregen uit een vervolgstudie van niet

groeivertraagde à terme extreem acidemisch ($pH_{na}$ < 7.00) geboren kinderen. Op twee en een half-jarige leeftijd deden deze kinderen het net zo goed als gematchte controles (Aarnoudse e.a. 1985).

In dezelfde groep van niet groeivertraagde kinderen, als die welke in Hoofdstuk 4 werden onderzocht, bleek de aanwezigheid van meconium in het vruchtwater als teken van asfyxie in het geheel niet gerelateerd te zijn aan de neonatale neurologische morbiditeit (Hoofdstuk 5). De Apgar scores na één en drie minuten vertoonden wel een verband, maar de percentages verklaarde variantie in NNOS waren, net als voor de bloedgasvariabelen, erg laag (<1%). De combinatie van de Apgar score met één van de pH-variabelen deed dit percentage stijgen tot 1,5%. De hoogste incidentie van neurologisch suspecte en abnormale kinderen, en de hoogste mediane NNOS waarden, werden waargenomen bij kinderen met een lage één-minuut-Apgar score maar met een normale $pH_{na}$. Deze onverwachte bevinding suggereert dat andere factoren dan hypoxie meespelen en tevens dat een lage Apgar score eerder een gevolg is van andere nadelig inwerkende factoren dan een indicator van hypoxie; een veronderstelling die tevens werd gedaan aan de hand van de British Survey Study uit 1970 (Peters e.a. 1984).

In deze onderzochte groep van niet groeivertraagde à terme geboren kinderen kan dus geconcludeerd worden (Hoofdstuk 4 en 5) dat asfyxie bij de geboorte niet verantwoordelijk is voor duidelijke neonatale neurologische afwijkingen. Dit betekent dat voor de meerderheid van de kinderen die neurologisch abnormaal waren (Tabel 1) geen oorzaken konden worden vastgesteld, alhoewel deze waarschijnlijk gezocht moeten worden onder de in Hoofdstuk 2 genoemde. In recente literatuur (Sims e.a. 1985; Paul e.a. 1986; Mann 1986) worden aanwijzingen gevonden dat reeds voor de bevalling veroorzaakte beschadiging van het centrale zenuwstelsel (CZS) niet zeldzaam is. Waarschijnlijk is tot nu toe bij veel van deze kinderen met zulke CZS-beschadigingen de terminologie "onverklaarde neurologische handicaps" toegepast. Het is een uitdaging voor de moderne obstetrie om de oorzaken van deze gevallen op te sporen, ze te herkennen en methoden ter preventie te ontwikkelen.

Bij groeivertraagde à terme geboren kinderen (Hoofdstuk 6), vooral als deze ernstig in groei waren achtergebleven en/of geboren via de keizersnede, werden vaker neonataal neurologische morbiditeit en asfyxie/hypoxie gevonden dan bij de niet groeivertraagde à terme geboren groep. Ernstig groeivertraagde kinderen blijken kwetsbaarder te zijn voor

hypoxie dan matig groeivertraagde kinderen. Het percentage variantie in NNOS verklaard door de combinatie van indices van asfyxie was in de eerstgenoemde groep drie maal zo hoog als in de laatstgenoemde (22% tegen 7%). Alhoewel iets hoger dan bij niet groeivertraagde à terme geboren kinderen, geven deze lage percentages bij groeivertraagde kinderen aan dat asfyxie bij de geboorte slechts weinig bijdraagt tot de neonataal neurologische morbiditeit. Bij de groeivertraagde à terme via de keizersnede geboren kinderen bleek dat de combinatie van verschillende gemeten asfyxie variabelen 93% van de variantie in NNOS verklaarden. De slechtere neurologische conditie in deze groep werd evenwel bepaald door kinderen bij wie "late" decelaraties in het cardiotokogram (CTG-15/23 = 61%) aanwezig waren. Wij veronderstellen dat deze tekenen van foetale hypoxemie, die meestal (79%) voor de geboorte reeds aanwezig waren, belangrijker zijn voor de neonataal-neurologische conditie dan de meer algemeen gebruikte tekenen van asfyxie bij de geboorte.

Hetzelfde werd gevonden bij groeivertraagde prematuur geboren kinderen (Hoofdstuk 7). Ook in deze groep correleerden de late decelaraties in het CTG (in 80% voor de geboorte aanwezig) beter met de neurologische conditie dan de Apgar score en/of de pH variabelen bij de geboorte. Verminderd neurologisch functioneren van deze kinderen kan daarom eerder worden toegeschreven aan "chronische" hypoxemie (en ondervoeding) dan aan "acute" asfyxie bij de geboorte. Deze redenering kan gedeeltelijk worden ondersteund door morfologische bevindingen bij groeivertraagde kinderen (Dobbing 1974) en in diermodellen (Bedi 1984), waarin veeleer kleinere hersenen en minder cellen zijn gevonden dan omschreven lesies, zoals meestal het geval is na ("acute") asfyxie (Kreusser en Volpe 1984). Ten aanzien van de reeds antenataal afwijkende foetale hartactiepatronen zijn onlangs vrijwel dezelfde bevindingen gepubliceerd door Lorentz e.a. (1986). Deze suggereren dat de in groei vertraagde foetus het beste geboren kan worden vóórdat antenataal reeds tekenen van hypoxemie verschijnen. De voordelen van vroeg ingrijpen moeten evenwel opwegen tegen de risico's van een vroege (premature) bevalling en de waarde van methoden om reeds vroeg die foetussen te herkennen die de kans lopen om intrauterien antenataal hypoxemisch te worden (bv analyse van de bloedstroomprofielen in de navelstreng) moet nog bevestigd worden. Gecontroleerde studies zijn noodzakelijk om deze vragen te beantwoorden.

Bij niet-groeivertraagde prematuur geboren kinderen bleek een relatie tussen asfyxie variabelen (speciaal de pH) en de neonataal-neurologische morbiditeit duidelijk aanwezig te zijn, hoewel minder uitgesproken dan in de groeivertraagde prematuren groep (Hoofdstuk 7). Aan de hand van gegevens die in dit hoofdstuk werden gepresenteerd kan worden benadrukt dat asfyxie tijdens de geboorte ook bij het niet-groeivertraagde premature kind zoveel mogelijk moet worden voorkomen. Eigenlijk was deze groep de enige waarin een duidelijk effect van asfyxie bij de geboorte kon worden gedemonstreerd (waarbij reeds voor de geboorte aanwezige "chronische" hypoxemie uitgesloten werd geacht). In tegenstelling tot wat anderen vonden blijkt de premature partus op zich niet tot hypoxie/acidemie te leiden.
Van alle 247 groeivertraagde à terme geboren kinderen (Hoofdstuk 6) en alle 126 premature kinderen (Hoofdstuk 7) waren volledige neurologische follow-up gegevens op vier tot zes-jarige leeftijd bekend (Hadders-Algra e.a. 1986). In de eerstgenoemde groep waren twee van de zes kinderen die bij de geboorte acidemisch ($pH_{na} < 7.10$) neurologisch abnormaal op vier tot zes-jarige leeftijd, en in de laatst genoemde groep vijf van de acht. In deze risicogroepen betekent dit dat in de helft van de 14 definitief afwijkende kinderen acidemie aanwezig was bij de geboorte. Dat in zes van deze zeven kinderen een abnormaal foetaal hartactiepatroon reeds antenataal aanwezig was benadrukt het gevaar van "chronische" hypoxemie.

## CONCLUSIES

In deze geselecteerde Nederlandse ziekenhuispopulatie kan geconcludeerd worden dat,

1. de meerderheid van de neonataal neurologisch abnormale kinderen niet groeivertraagd en niet prematuur is;
2. bij niet groeivertraagde à terme geboren kinderen "asfyxie bij de geboorte" geen hoofdoorzaak is van neurologische afwijkingen bij de pasgeborene;
3. bij groeivertraagde kinderen chronische ondervoeding (chronische hypoxemie meegerekend) belangrijker lijkt voor de neurologische conditie dan de actuele conditie bij de geboorte;
4. asfyxie bij de geboorte gerelateerd is aan neurologische beschadigingen bij niet groeivertraagde prematuur geboren kinderen.

# DANKWOORD

Dit proefschrift kwam tot stand in de Kliniek voor Obstetrie en Gynaecologie van het Academisch Ziekenhuis te Groningen (destijds hoofd: Prof.Dr J. Janssens, thans Prof.Dr H.J. Huisjes). De studie maakte deel uit van het Groninger Perinataal Project. Dit project kwam mede tot stand dankzij de vruchtbare samenwerking met de afdeling Ontwikkelingsneurologie van de Rijksuniversiteit te Groningen (hoofd: Prof.Dr H.F.R. Prechtl) en kon worden uitgevoerd dankzij subsidie verleend door het Preventiefonds en het Prinses Beatrixfonds.

Allen die direkt of indirekt hebben bijgedragen aan het tot stand komen van dit proefschrift ben ik zeer erkentelijk. Met name wil ik bedanken:

- Prof.Dr H.J. Huisjes, voor zijn wetenschappelijke kennis en zijn optimale en kritische begeleiding bij het schrijven van dit proefschrift.
- Prof.Dr. B.C.L. Touwen, onder wiens inspirerende supervisie het neurologisch onderzoek destijds werd verricht. Zijn hulp en begeleiding, met name op het gebied van de Ontwikkelingsneurologie was onmisbaar.
- Dr G.H.A. Visser, voor zijn immer aanwezige optimisme en uithoudingsvermogen. Gerard, jouw enthousiasme deed ons spelender wijze in deze materie rollen. Dat dit "spelletje" tot dit resultaat heeft geleid is voornamelijk jouw verdienste geweest.
- Anita Olinga, voor verreweg het meeste computer werk. Anita, zonder jouw hulp zou ik nu nog blind achter een computer hebben gezeten. Ik hoop dat je begrijpt dat dit werk mij de laatste jaren te veel werd.

Verder wil ik bedanken

- Dr V. Fidler, voor zijn statistische ondersteuning.
- J. Pleiter, voor het tekenen en fotograferen van de figuren.
- Dr J.G. Aarnoudse, met wiens hulp een deel van Hoofdstuk 2 (2.5 en 2.6) tot stand kwam.
- Drs M. Hadders-Algra, van wie ik de follow-up gegevens uit het Groninger Perinatal Project verkreeg.
- Mw J. Abma-Hill, voor de deskundige hulp bij het corrigeren van het Engels en het op de tekstverwerker zetten van een deel van dit manuscript.
- Riekje Canus, voor haar hulp bij het typewerk van enige artikelen.
- Cesia Koppe, Sjaak Wijma en Alof Canrinus, degenen die mij op het

laatste moment uit de nood hielpen met het lay-outen van het manuscript.

Tenslotte wil ik bedanken, mijn moeder, wijlen mijn inspirerende vader, Janette en Marties. Janette, de onzekerheid omtrent waar wij onze nabije toekomst moeten opbouwen, de recente verhuizing en dit veel te veel tijd en energie opeisende proefschrift, hebben jou hopelijk niet al te veel gekwetst.